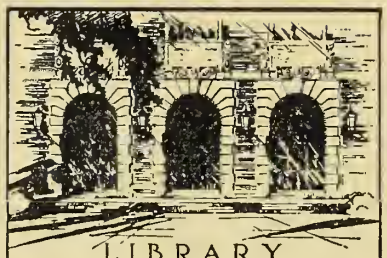


SEMINAR TOPICS

I Semester 1945-46

THE EFFECTS OF STERIC STRAIN ON BASE STRENGTH

H. C. Brown, Wayne University

In the Lewis generalized concept of acids and bases, a substance which can coordinate with a pair of electrons is considered an acid, one which has such a pair available is considered a base.

$$H^+ + :\ddot{\underset{..}{O}}:H^- \rightarrow HOH$$

$$F_3B + OR_2 \rightarrow F_3\overset{-}{B} - \overset{+}{O}R_2$$

$$R_3B + NR_3 \rightarrow R_3\overset{-}{B} - \overset{+}{N}R_3$$

(acid) (base)

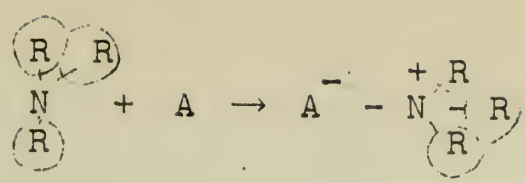
The general influence of factors such as "inductive" and "resonance" effects on acid and base strength have been well established. Thus the "inductive" effect accounts for the greater acidity of boron fluoride as compared to trimethyl boron and the greater basicity of methyl amine as compared to ammonia.

$$\begin{array}{c} F \\ \uparrow \\ F \leftarrow B \\ \downarrow \\ F \end{array} \quad \text{and} \quad \begin{array}{c} CH_3 \\ \downarrow \\ H_3C \rightarrow B \\ \uparrow \\ CH_3 \end{array}$$

$$NH_3 \quad \text{and} \quad CH_3 \rightarrow NH_2$$

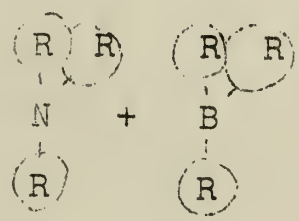
The influence of "resonance" has been used to account for the acidity of carboxylic acids and phenols.

During the past three years, Brown has published a series of papers papers accounting for many puzzling observations on relative base strength on the basis of the general nature of steric effects. For example, it would be predicted that the "inductive" effect increasing the strength of methylamine should be additive in dimethyl amine and trimethylamine. Dimethylamine is indeed a stronger base but trimethyl amine is actually weaker than methylamine. Brown has pointed out that the nitrogen atom, after coordination with an acid, must be tetrahedral. This involves bringing the three groups already on the nitrogen closer together than they were in the essentially planar free base. Therefore, if these groups are large and bulky enough, there may be a steric repulsion tending to hinder formation of the tetrahedral salt. This type of steric strain, acting at the "back" of the molecule, has been termed "B-strain" by Brown and is independent of the reference acid coordinating with the base.

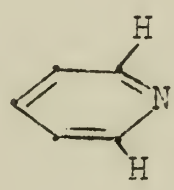


The relative base strengths tetrahydrofuran >> dimethyl ether > diethyl ether > diisopropyl ether have also been accounted for on the basis of B-strain, the cyclic compound being restricted in a configuration favorable for coordination with boron fluoride.

Another steric effect which has been clearly demonstrated is that involved in the reaction of a bulky acid (A) with a bulky amine in which the groups in the two entities may retard coordination by a direct ("front") interference; this has been designated "F-strain" by Brown.

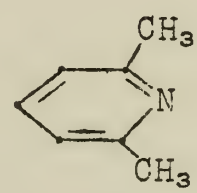


An early example may be taken from measurements of the relative base strength of pyridine (I) and α,α-lutidine (II).



I

and



II

Because of the inductive effect of the methyl groups, II is of slightly stronger base than I to hydrogen chloride. Using the bulkier acid, boron fluoride, II is a much stronger acid than I. Toward HCl, HBr, BF_3 or BH_3, trimethylamine is a stronger base than pyridine but with $B(CH_3)_3$ the reverse is true.

Another study of F-strain was made by comparing the base strengths of ammonia (III) and trimethyl amine (IV) toward four trialkyl borons (V) by analysis of free amine recovered from a mixture of one equivalent each of (III), (IV) and (V).

$$\underset{\text{IV}}{(CH_3)_3N} + NH_3 \cdot BR_3 \rightleftarrows (CH_3)_3H \cdot BR_3 + \underset{\text{III}}{NH_3}$$

R	IV	III
CH_3	15%	85%
C_2H_5	91%	9%
$(CH_3)_2CH$	96%	4%
$(CH_3)_3C$	98%	-

Further data on relative base strengths is summarized in Fig. 1.

Curve A. Predicted from inductive effect alone.
Curve B. R = CH_3; acid. H^+, $B(CH_3)_3$ or R = Et; acid = H^+.
Curve C. R = Et; acid $B(CH_3)_2$
Curve D. R = CH_3; acid = $B(\underline{t}\text{-Bu})_3$
Curve E. R = Et; acid = $B(\underline{t}\text{-Bu})_3$

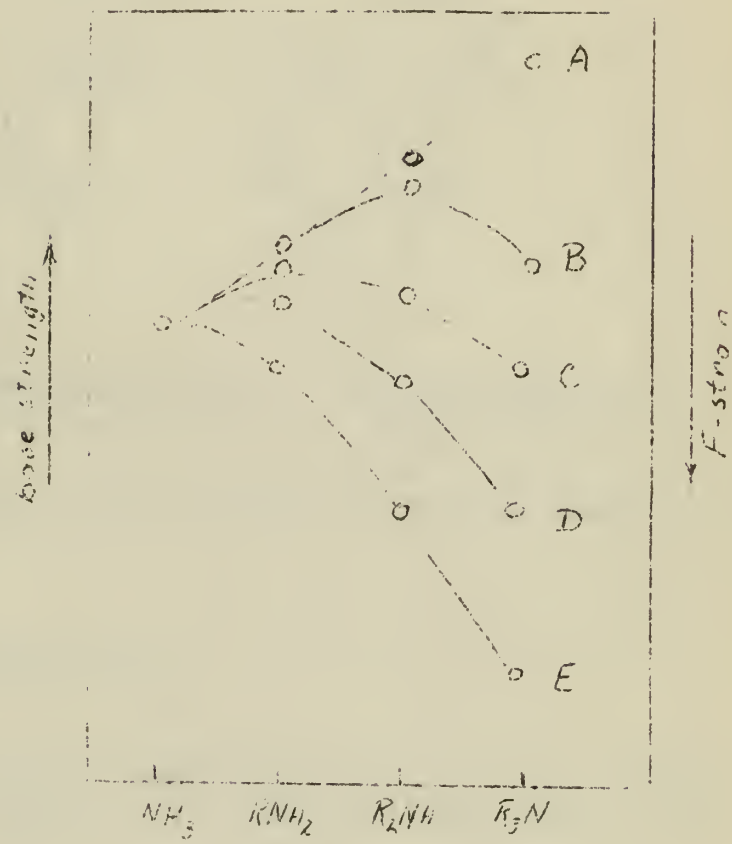


Fig 1.

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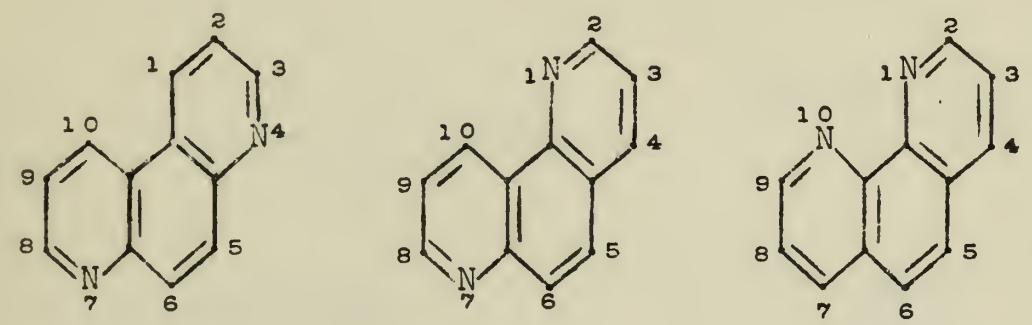
Reported by C. C. Price
October 10, 1945

PHENANTHROLINES

Phenanthrolines have the same structure as phenanthrene with two carbon-hydrogen groups in the two non adjacent rings replaced by nitrogen. This seminar will deal with those phenanthrolines which are structurally related to the phenylenediamines. Hence there are three possible isomers.



I II III

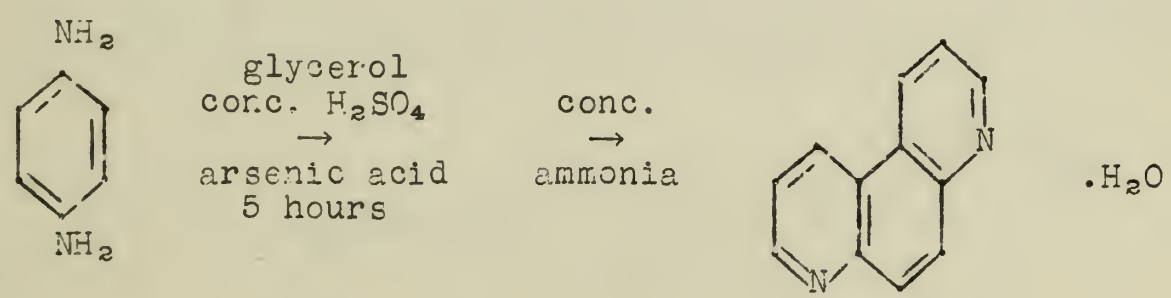
p-phenanthroline (4,7-phenanthroline) m-phenanthroline (1,7-phenanthroline) o-phenanthroline (1,10-phenanthroline)

The above system of naming is that used by Chemical Abstracts.

p-Phenanthrolines

There are a variety of methods that have been used to prepare p-phenanthroline. In all the examples the Skraup reaction is used on the appropriate starting material.

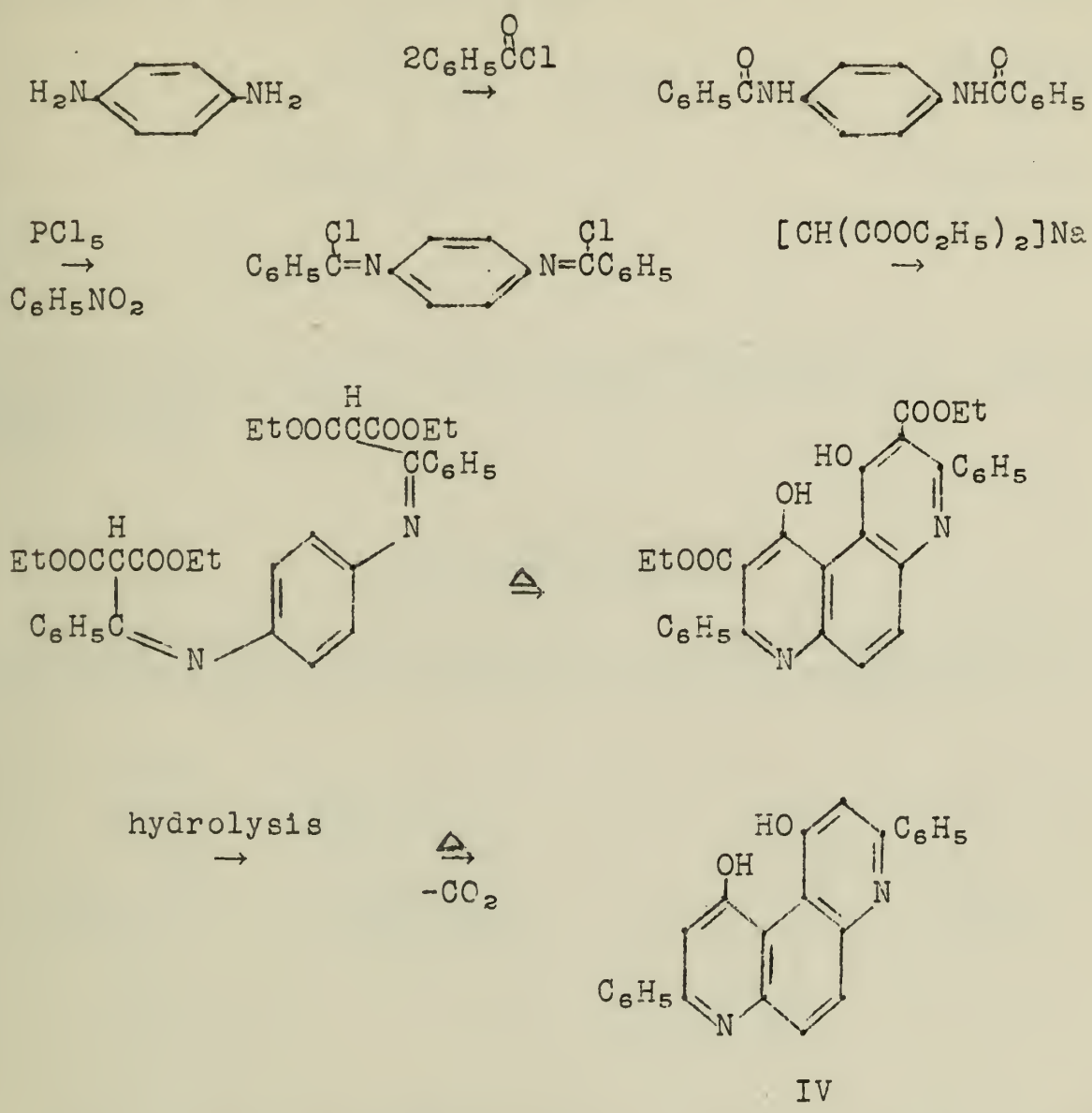
A double Skraup reaction on p-phenylenediamine gives a 60% yield of the hydrate of p-phenanthroline.



Good yields of p-phenanthroline can also be obtained from a Skraup reaction using 6-aminoquinoline, p-amino-azobenzene or a mixture of p-phenylenediamine and p-nitroaniline.

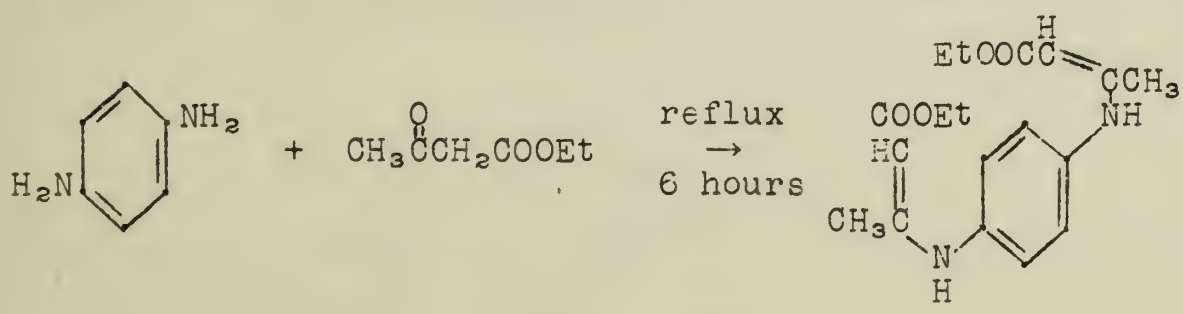
p-Phenanthroline forms both a mono and a di-methiodide. It gives a yellow precipitate with ferric chloride.

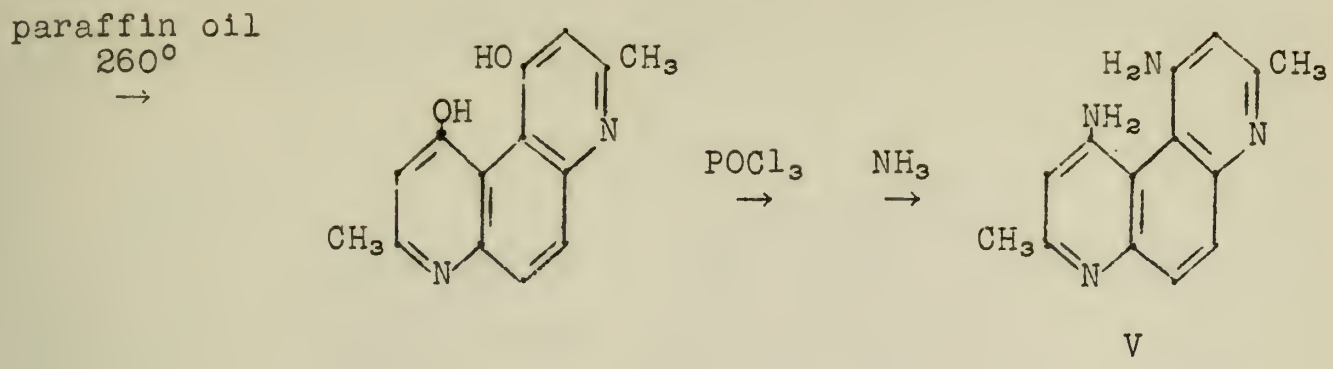
A large number of substituted p-phenanthrolines have been prepared. Rao and Wheeler have synthesized 1,10-dihydroxy-3,8-diphenyl-4,7-phenanthroline (IV) by the following method.



IV

The Conrad-Limpach reaction has been used in the synthesis of 1,10-diamino-3,8-dimethyl-4,7-phenanthroline (V).

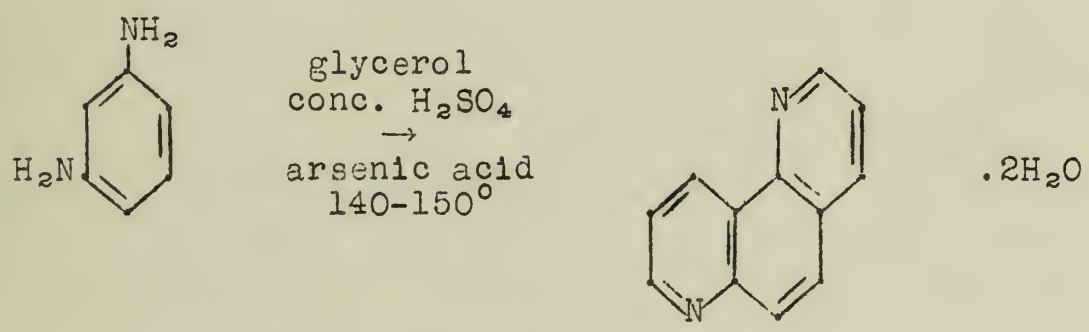




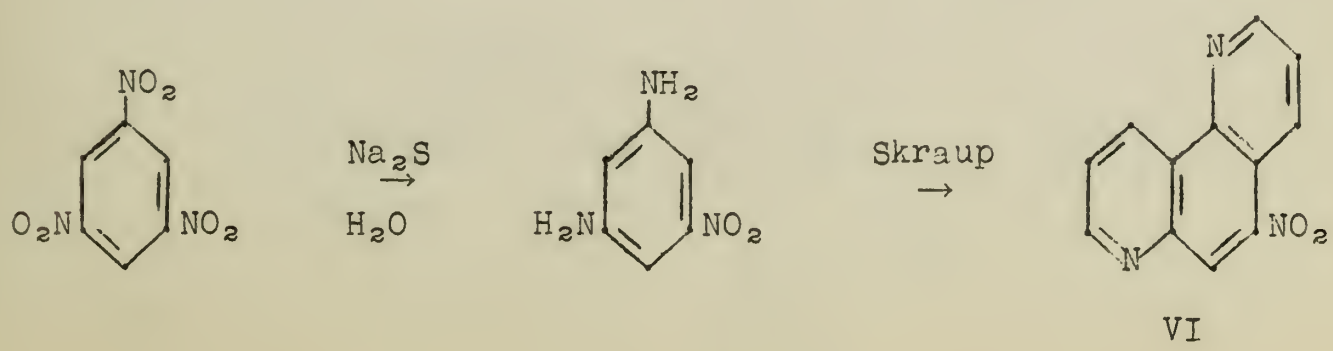
The chloro derivatives of phenanthrolines have been treated with different types of alkyl amines in attempts to find new antimalarials.

m-Phenanthrolines

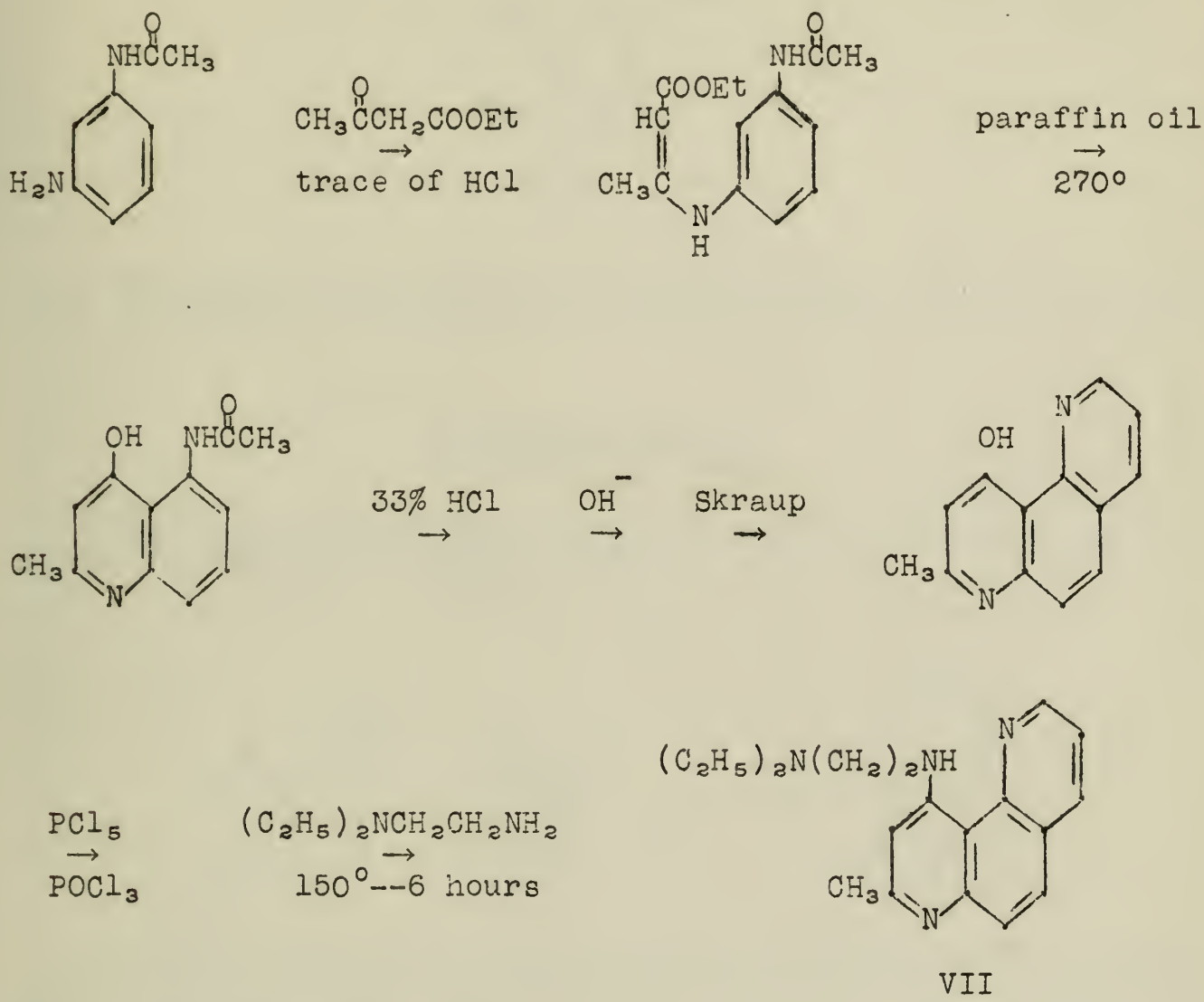
A 50% yield of the dihydrate of m-phenanthroline has been obtained by the Skraup reaction on m-phenylenediamine.



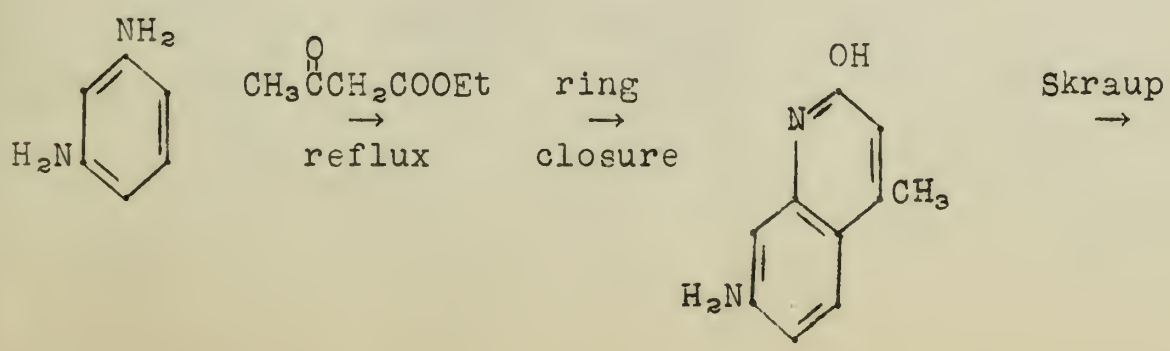
Korczynski and Brydowna have synthesized 5-nitro-1,7-phenanthroline (VI) in a 43% yield by starting with trinitrobenzene, reducing it to the diamine and then carrying out a double Skraup reaction.

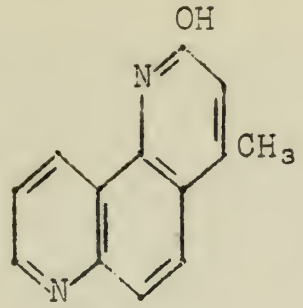


Kermack and Webster have synthesized m-phenanthrolines with substituents in the nitrogen containing ring as possible anti-malarials. They prepared 10-(β-diethylaminoethylamino)-8-methyl-1,7-phenanthroline (VII) as follows:



A different product was obtained under similar conditions when m-phenylenediamine was used in place of m-aminoacetanilide. The ester rather than the keto group reacted with the amine and ring closure went in the 4 rather than the 2 position.



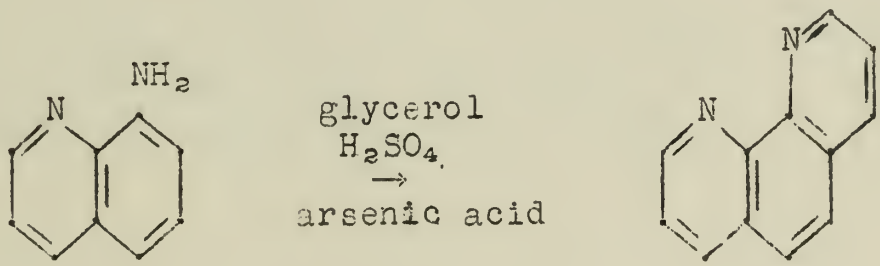


VIII

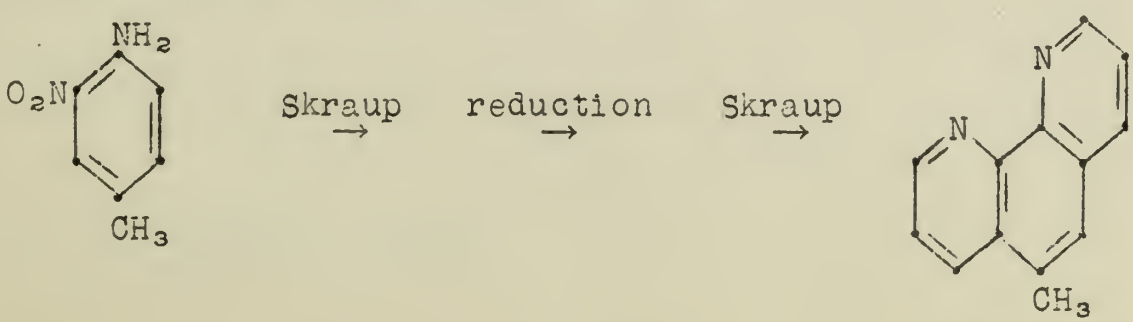
The 2-hydroxy-4-methyl-1,7-phenanthroline (VIII) was treated with phosphorus oxychloride and various amino derivatives prepared.

o-Phenanthrolines

The usual preparative method for o-phenanthroline is the Skraup reaction on 8-aminoquinoline.



The Skraup reaction on 1,2-phenylenediamine or on 1,2-phenylenediamines suitably substituted in either the 4 or (5) positions give practically none of the desired product. However application of the method of Skraup to suitably substituted 2-nitroanilines followed by reduction to the 8-aminoquinoline and then a second Skraup can be carried out successfully. 5 (6) Methyl-1,10-phenanthroline (IX) is prepared this way.



IX

The 5-chloro and 5-bromo derivatives can be synthesized in the same manner.

o-Phenanthroline forms complexes with many metallic ions. The o-phenanthroline-ferrous ion is used as an oxidation reduction indicator. The base dissolves easily in solutions of ferrous salts, three molecules combining with one ferrous ion. The complex ferrous ions are red in color. Strong oxidizing agents such as potassium permanganate in acid solution oxidize the ferrous complex to a ferric one, which is blue in color. The red ferrous complex is regenerated by reducing agents.

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Reported by Herbert E. Freier
October 17, 1945

BIOLOGICALLY IMPORTANT IMIDAZOLES

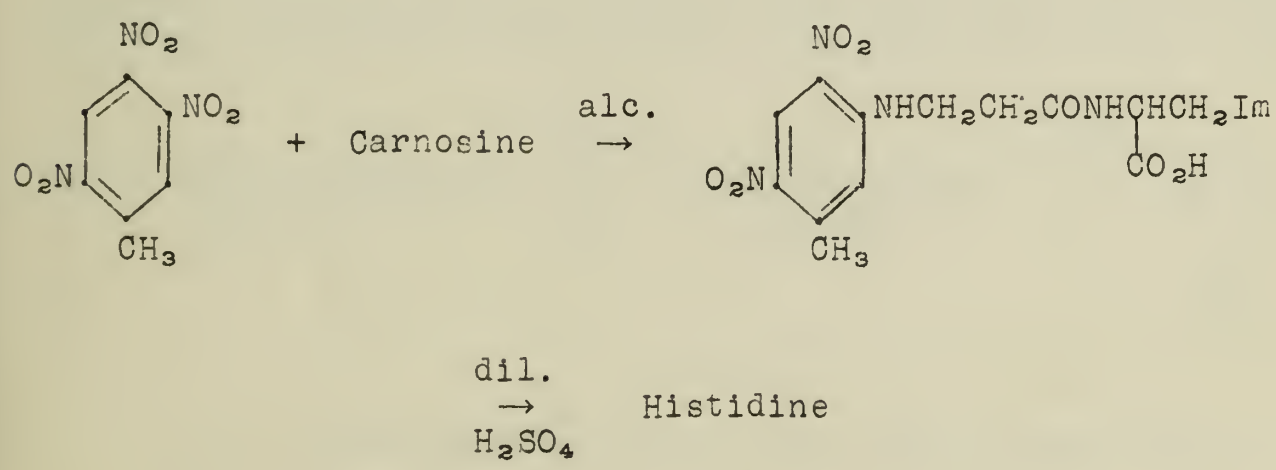
Anserine.--In 1929 Ackerman and coworkers announced the discovery of a new nitrogenous component of goose muscle. The compound, $C_{10}H_{16}O_3N_4$, was basic, showed properties resembling those of a peptide. In the same year Linneweh, Keil, and Hoppe-Seyler solved most of the problems of the structure of anserine. Reaction with nitrous acid indicated one primary amino group. The compound did not decolorize permanganate solution. After heating anserine with soda lime in an atmosphere of hydrogen 1,5-dimethylimidazole was isolated. These data established the presence of an imidazole ring, the location of the N-methyl group, and indicated that anserine was monomethylated carnosine.

Hydrolysis with barium hydroxide yielded methylhistidine and beta-alanine. The order of attachment of the amino acids was established by Keil who condensed the peptide with gamma-TNT and hydrolysed the resulting compound to produce dinitrotoluyl alanine. Hence the structure was established.

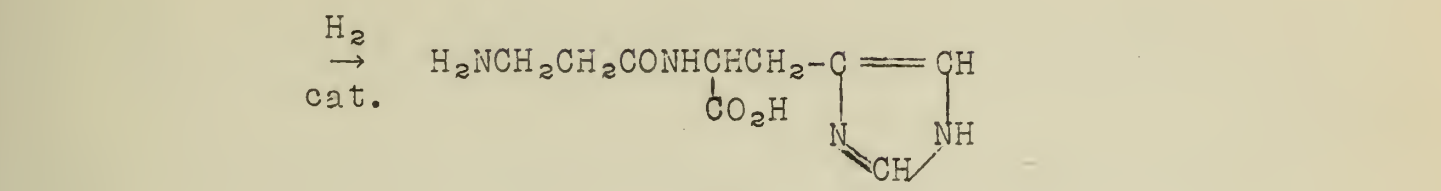
Anserine has been synthesized by condensing beta-alanine with 1-N-methylhistidine.

Carnosine.--Hydrolysis of carnosine with barium hydroxide produced histidine and beta-alanine. Baumann and Ingwaldsen showed the order of attachment of the amino acids by deaminating the peptide. From the deaminated product a 70 percent yield of histidine was isolated, indicating that carnosine is beta-alanyl-histidine.

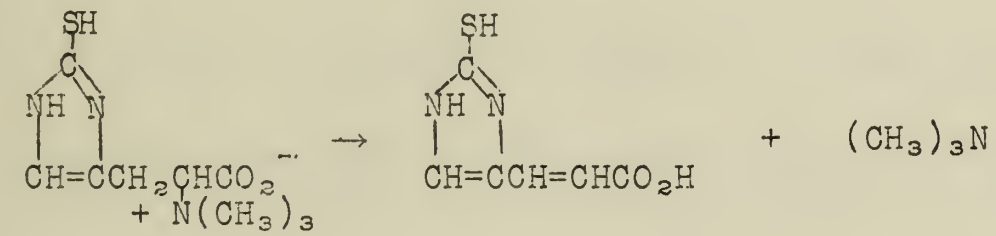
Barger and Tutin also showed the structure of carnosine by condensing gamma-TNT with carnosine and hydrolysing the resulting compound to produce histidine.



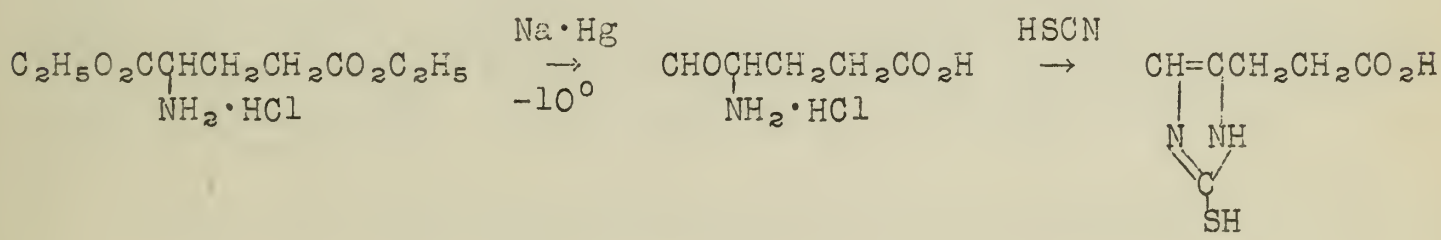
In 1935, Sifferd and du Vigneaud obtained carnosine from histidine in 65 percent over-all yield.



Ergothioneine.--Practically all of the work published on the structure of ergothioneine is contained in a paper by Barger and Ewins. The empirical formula is $C_9H_{15}O_2N_3S$. Color reactions and empirical formula indicated the presence of an imidazole ring and a betaine group. Heating with concentrated potash cleaved ergothioneine to trimethylamine and a yellow acid, $C_6H_5O_2N_2S$.



Oxidation of the mercaptyl group of the yellow acid, followed by reduction, gave beta-imidazolypropionic acid. Oxidation of the original compound with iodine produced a disulfide. The position of the sulfhydryl group on the ring was confirmed by Akabori, who prepared thiolimidazole propionic acid, identical with the product of reduction of Barger and Ewins' thiolimidazolylacrylic acid.



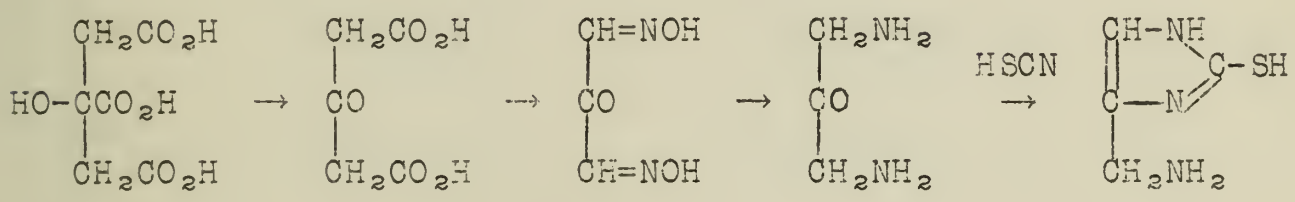
As yet ergothioneine has not been synthesized successfully.

Histamine.--Windhaus and Knoop have prepared this important amine by the following method.

$$CH_3COCH_2CH_2CO_2H \rightarrow CH_2BrCOCHBrCH_2CO_2H \xrightarrow{Ag_2CO_3} CHOCOCH_2CH_2CO_2H$$

$$\xrightarrow[HCHO]{NH_3} ImCH_2CH_2CO_2H \rightarrow ImCH_2CH_2CON_3 \rightarrow ImCH_2CH_2NH_2$$

Pyman has developed another synthesis, using citric acid.



$$\xrightarrow{HNO_3} ImCH_2OH \rightarrow ImCH_2Cl \rightarrow ImCH_2CN \rightarrow ImCH_2CH_2NH_2$$

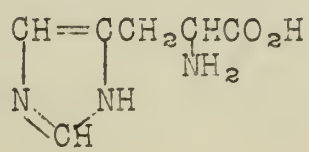
During the oxidation of the thiolimidazole, nitrous acid is formed which converts the terminal amino group to a hydroxyl group.

Histidine.--By means of a critical review of previous work and a few well-chosen experiments Pauly determined the structure of this amino acid. The empirical formula is $C_6H_9N_3O_2$. Heating the hydrochloride above its melting point evolved carbon dioxide, indicating the presence of a carboxyl group. Sodium hypobromite removed one nitrogen atom, and two molecules of benzenesulfonyl chloride reacted with one molecule of histidine. Hence one nitrogen was primary, one was secondary, and one was tertiary. The empirical formula indicated two double bonds or a triple bond. Since only one nitrogen was tertiary, one double bond must be between carbon atoms. Stability of the molecule indicated a conjugated ring system. Pauly proposed the structure which is currently accepted.

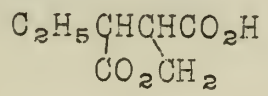
Pyman has synthesized the amino acid from chloromethylimidazole.

$$ImCH_2Cl + CClNa(CO_2C_2H_5)_2 \rightarrow ImCH_2CCl(CO_2C_2H_5)_2$$

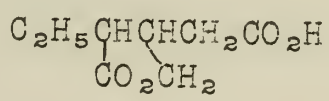
$$\rightarrow ImCH_2CHClCO_2H \rightarrow$$



Pilocarpine.--The elucidation of the structure of this alkaloid resulted principally from the work of Jowett and of Pinner and Schwarz. The empirical formula is $C_{11}H_{16}O_2N_2$. Heat converted it to its stereoisomer, isopilocarpine. Structural studies were made on the latter compound. Oxidation with permanganate yielded pilopic acid, $C_7H_{10}O_4$, and its homolog, homopilopic acid, $C_8H_{12}O_4$, and a small quantity of methylurea. Titration of pilopic acid indicated that it was a lactone, and further oxidation produced butyric acid. Jowett has proposed the structure of this acid and its homolog.



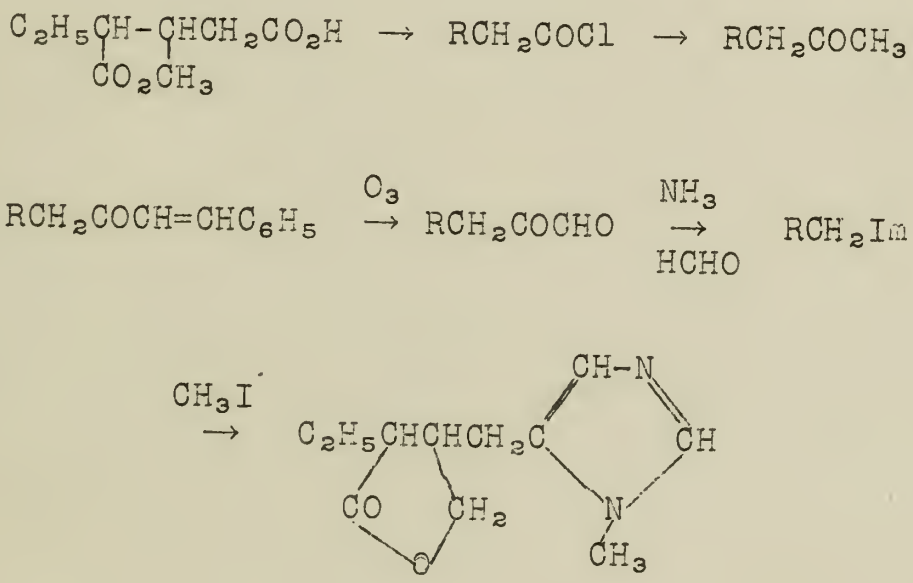
Pilopic acid



Homopilopic acid

Heating pilocarpine with soda lime produced 1,5-dimethylimidazole and 1-methyl-5-n-amylimidazole. On the basis of these facts Pinner and Schwarz proposed the structure of pilocarpine.

Dey has developed a synthesis of pilocarpine and isopilocarpine.



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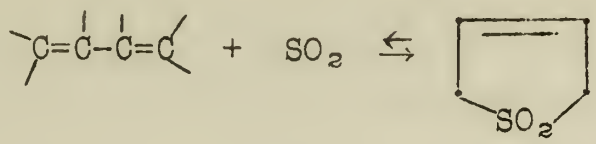
Reported by J. H. Saunders
October 17, 1945

REACTIONS OF UNSATURATED CYCLIC SULFONES

H. J. Backer, University of Gottingen

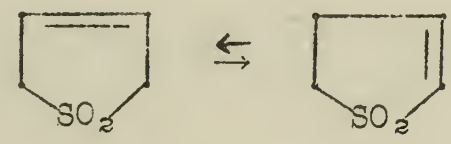
Preparation.--In general the reaction of sulfur dioxide with a conjugated diene produces an unsaturated cyclic sulfone.



This reaction can be reversed by heating. Many substituted butadienes have been used in this reaction, which has failed with only a few of them, such as cis-cis-1,4-dicarboxy-1,3-butadiene. The reduction of thiophene sulfones and the oxidation of the appropriate sulfides with hydrogen peroxide, also give these unsaturated sulfones

Most of the reactions of this structure arise from the fact that it has (1) a carbon to carbon double bond, and (2) active hydrogen in the alpha positions.

Isomerization of the double bond.--In alkaline solution, with ultraviolet light, many of these sulfones isomerize. It was at first thought that this was a cis-trans phenomenon, but, by ozonizing the products, it was discovered that the double bond had moved from the 3,4 to the 2,3 position.

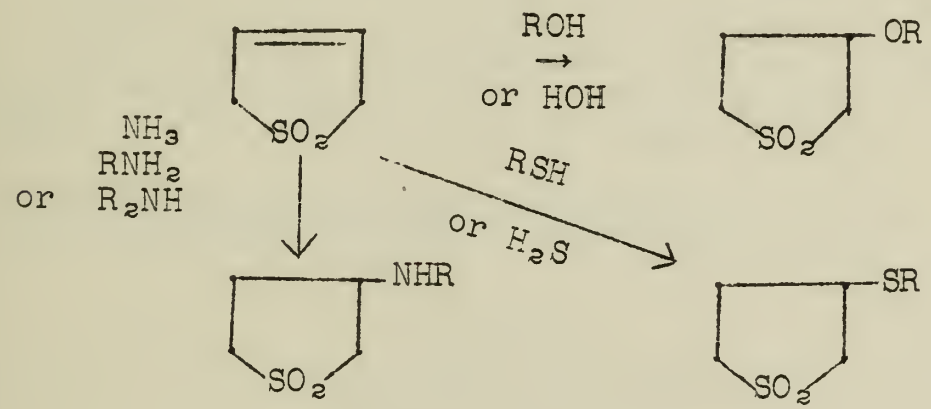


It has also been found that this is a matter of equilibrium, and, while the ultraviolet light speeds up the reaction, it does not affect the composition of the equilibrium mixture, which usually favors the 2,3-form. The mechanism of this rearrangement has been thought to involve the 3-hydroxy cyclic sulfone, as an intermediate. However, this has been synthesized, and it is stable under the conditions used. It has been suggested that the shift merely involves the hydrogen and the double bond.

There is a general tendency, in this cyclic sulfone system, to avoid having two double bonds in the ring. Thus the second double bond will, if possible, take up a position between the ring and a substituent.

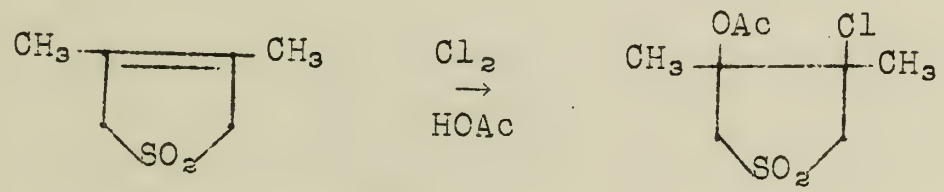
In addition, in the thiophene solfones which have been made, the reduction of the first double bond is much easier than the reduction of the second. However, the saturated compound is a little less stable than the compound with one double bond in the ring.

Addition of unsymmetrical reagents.--In basic solution alcohols and amines add to the double bond in good yields, forming saturated cyclic sulfones, substituted in the three position. The reaction with mercaptans gives lower yields.



Backer considers that isomerization may take place before the addition because some of the isomer is found whenever the reaction is incomplete. However, he also found that tertiary amines did not isomerize the sulfones.

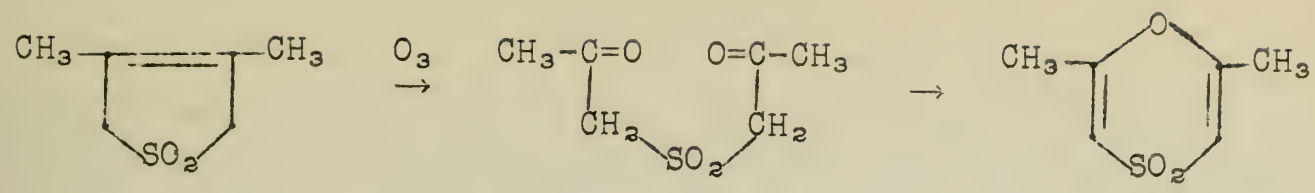
Chlorine in acetic acid solution has been used to give the addition of acetyl hypochlorite to the double bond.



Addition of symmetrical reagents.--The double bond in these sulfones will add bromine, although slowly if large substituents such as tertiary butyl groups are in the 3,4-positions.

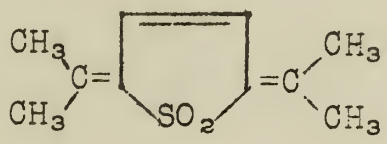
Hydrogenation can be effected catalyticly with nickel and silicic acid, palladium or platinum catalysts.

Ozone will attack the double bonds in these compounds and this reaction has often been used as structure proof. In some cases where a diketone is formed, there is dehydration to form a cyclic ether.



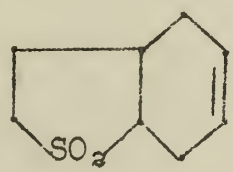
Peracetic acid gives a mixture of the diacetate and the monoacetate of the corresponding glycol, but lead tetraacetate, osmic acid or potassium permanganate give the glycol itself. Treatment of the mono or diacetate with alkali gives an oxide which is difficult to hydrolyze in some cases. Deactivation of the double bond by the sulfone group is illustrated by the fact that potassium permanganate and lead tetraacetate do not act on double bonds which are alpha to one sulfone group or beta to two.

Miscellaneous reactions.--Butadiene sulfone reacts with acetone in a basic solution to form a condensate.

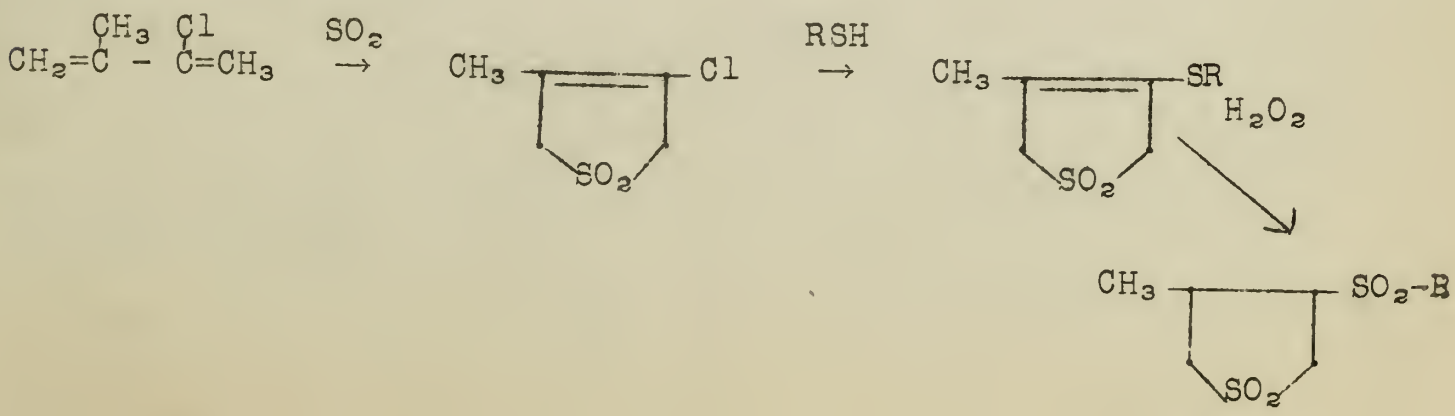


The sulfones also liberate methane from methylmagnesium iodide, which is presumably another reaction of the active alpha hydrogen.

The isomer of butadiene sulfone, having the double bond in the 2,3-position has been used in Diels Alder reactions, for instance with butadiene.



The sulfone from 2-chloro-3-methyl-1,3-butadiene gives replacement reactions with mercaptans, the products of which can be oxidized to disulfones



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I. G. Farbenindustry, A.-G. Britt., 489,974, August 8, 1938, C. A., 33,644 (1939); Fr., 847,254, October 5, 1939, C. A., 35,5519 (1941).

Reported by R. R. Chambers
October 24, 1945.

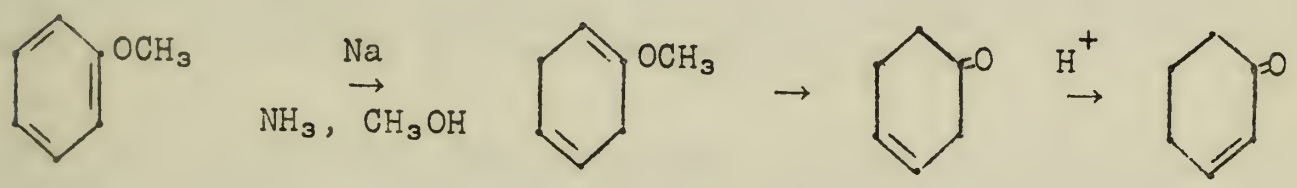
SOME NOVEL INTRODUCTION OF α,β-UNSATURATION

I. Arthur J. Birch, Oxford
II. Hans Rupe, Basel

I. In the first of a series of papers entitled "Reduction by Dissolving Metals", Birch reported experiments from which he determined the effect of a ready proton source, such as simple alcohols, on the course of the reduction of aromatic nuclei by alkali metals and liquid ammonia.

The products obtained from aromatic hydrocarbons by the action of alkali metals and liquid ammonia alone are the dihydro derivatives. The same dihydro derivatives were also obtained from the unsubstituted and alkyl substituted hydrocarbons when alcohols were added to the mixture. However, the methoxy substituted aromatic compounds gave unsaturated cyclic ketones which in every case were readily isomerized to cyclic α,β-unsaturated ketones by heating with dilute sulfuric acid. Thus, anisole gave 3-cyclohexenone which gave 2-cyclohexenone on isomerization.

Birch proposed the following mechanism to explain the formation of these products.



The demethylation of certain aromatic methyl ethers with alkali metals and liquid ammonia has been reported by Freudenberg, Lautsch and Piazolo.

In Table I are listed the compounds studied and their reduction products. The structure of the intermediates, which are not indicated, are based on absorption spectra measurements and the assumption that the bond isomerization to the final product proceeds by the shortest route. The structures of the final products are based on comparison of the semicarbazones with authentic samples. The structures of the two compounds marked (?) are assigned by analogy.

TABLE I

Compound Reduced	Product	Yield	Alcohol Used
Anisole	2-Cyclohexenone	20%	EtOH
2-Methyl anisole	6-Methyl-2-cyclohexenone	12%	EtOH
3-Methyl anisole	3-Methyl-2-cyclohexenone	42%	EtOH
4-Methyl anisole	4-Methyl-2-cyclohexenone	33%	MeOH
2,6-Dimethyl anisole	2,6-Dimethyl-2-cyclohexenone	10%	EtOH
2,5-Dimethyl anisole	3,6-Dimethyl-2-cyclohexenone(?)	15%	MeOH

SOME NEWER INTRODUCTION OF [illegible]

I. Arthur J. Birch, [illegible]
II. Hans Suge, Brazil

In the first of a series of [illegible] "Living Models", Birch reports experiments [illegible] demonstrated the effect of a [illegible] source, [illegible], on the course of the reduction [illegible] of aromatic metals and liquid ammonia.

The products obtained [illegible] from treating hydrogen [illegible] metals and liquid ammonia alone are the alkylbenzenes. The same [illegible] analyses were also obtained [illegible] substituted and alkoxy hydrocarbons which [illegible] to the mixture. However, the methoxy substituted compounds give [illegible] cyclic ketones which in [illegible] readily hydrolyze in acid, [illegible] with dilute aqueous solution. [illegible] 3-cyclohexenone [illegible] 2-cyclohexenone [illegible].

Birch proposed [illegible] following mechanism to [illegible] in [illegible] of these products.

[illegible] The structure [illegible] established by analysis.

TABLE I

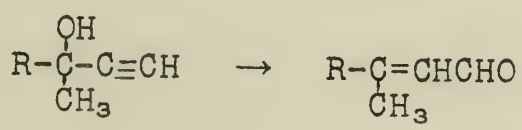
Compound Prepared	Reagent
Anisole	[illegible]
2-Methyl anisole	[illegible]
3-Methyl anisole	[illegible]
4-Methyl anisole	[illegible]
2,4-Dimethyl anisole	2,3-[illegible]
2,5-Dimethyl anisole	3,5-Dimethyl-4-[illegible]

2,4-Dimethyl anisole	4,6-Dimethyl-2-cyclohexenone	22%	MeOH
3,4-Dimethyl anisole	3,4-Dimethyl-2-cyclohexenone(?)	35%	MeOH
3,5-Dimethyl anisole	3,5-Dimethyl-2-cyclohexenone	16%	EtOH
1-Methoxy-5,6,7,8-tetrahydronaphthalene	Bicyclo(4,4,0)-1,6-decene-2-one	trace	EtOH
2-Methoxy-5,6,7,8-tetrahydronaphthalene	Bicyclo(4,4,0)-1,2-decene-3-one	44%	MeOH
5-Methyl indan	Bicyclo(4,3,0)-1,2-nonene-3-one	30%	EtOH
3-Methyl-6-isopropyl-anisole	3-Methyl-6-isopropyl-2-cyclohexenone	small	MeOH

On the basis of these reactions and others in the literature, Birch proposed a rule by which the products of this reduction can be predicted. "If a benzene ring bearing methoxy or alkyl groups (or the ends of a saturated ring) is written in the Dewar formulae in which the bridgehead is not occupied by a methoxyl group the chief product will correspond to the formula having the least substitutients at the bridgeheads."

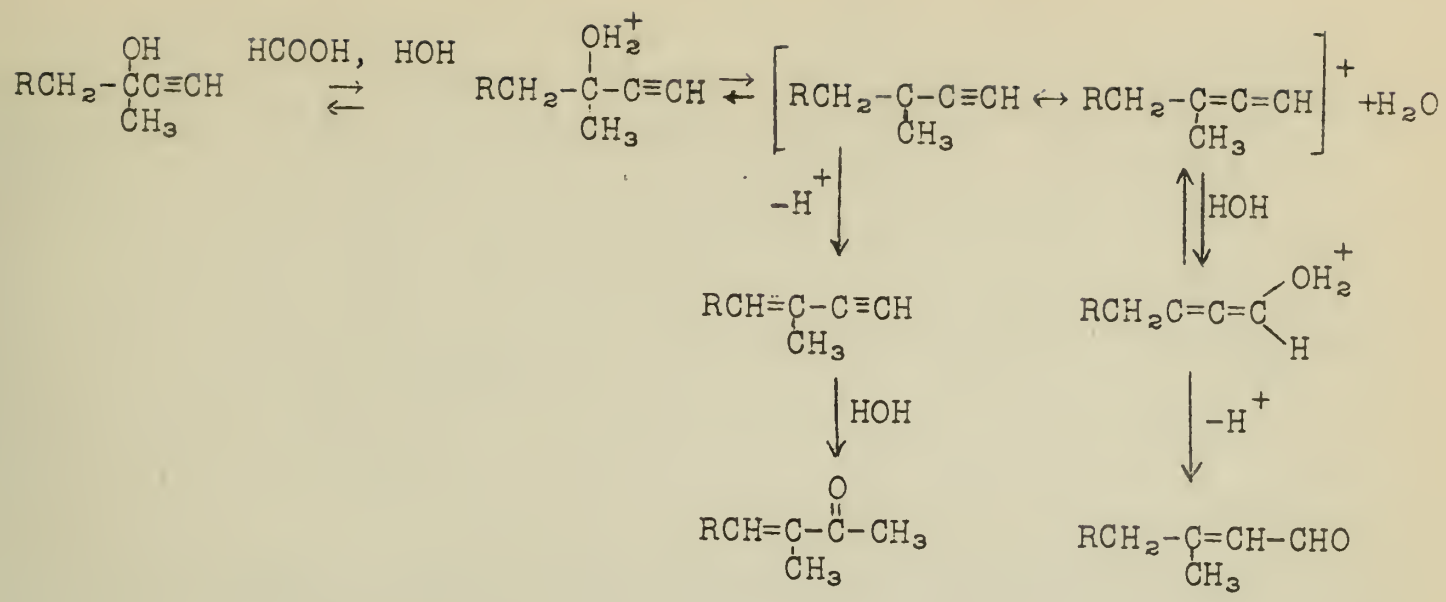
The scope of this reaction is limited by the solubility of aromatic compounds in liquid ammonia since the reduction process must compete with the tendency for the evolution of hydrogen. The addition of solvent ether aids the formation of a homogenous mixture with difficulty soluble compounds.

II. In 1926 Hans Rupe published a short paper in which he claimed, without presentation of any experimental evidence, the rearrangement of several acetylene carbinols to the corresponding α,β-unsaturated aldehydes according to the following scheme.



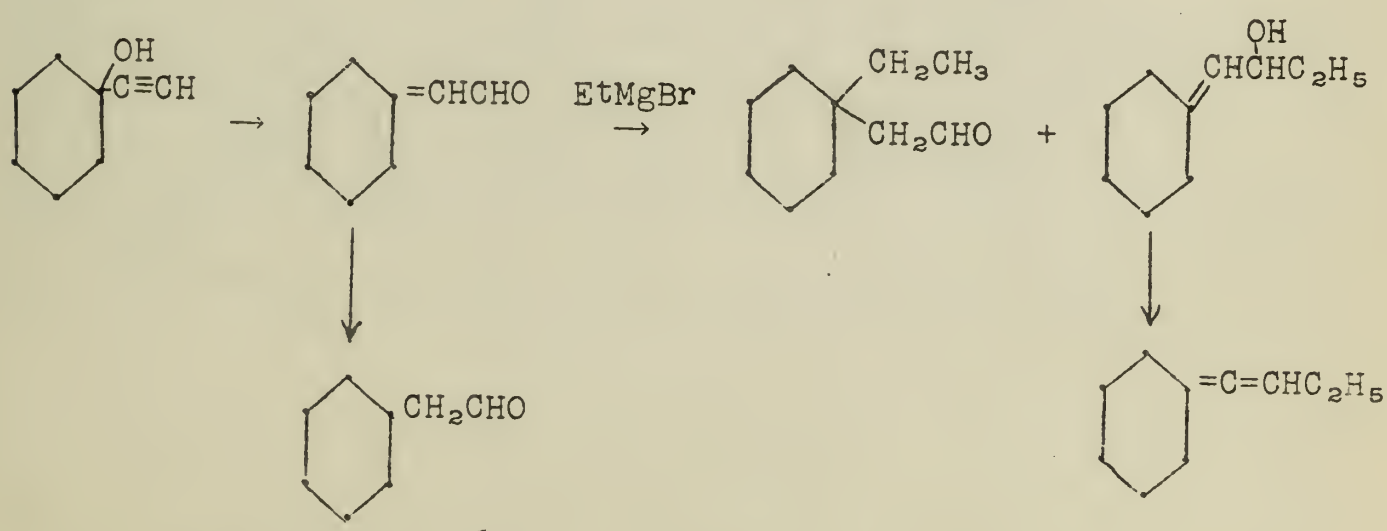
Several papers appeared during the next ten years in which the structure of these and several other unsaturated carbonyl compounds were discussed individually. Structures ranging from α,β- and β,γ-unsaturated aldehydes to α,β-unsaturated methyl ketones in which alkyl groups have been rearranged were assigned based upon experimental evidence which was often inconclusive. A critical examination of the experimental evidence presented in these papers, coupled with experiments conducted in this laboratory, leads to the conclusion that the principal products of these rearrangements must have been α,β-unsaturated ketones.

A reasonable mechanism which can account for the formation of both the α,β-unsaturated methyl ketones and the possible formation of the α,β-unsaturated aldehydes is as follows.

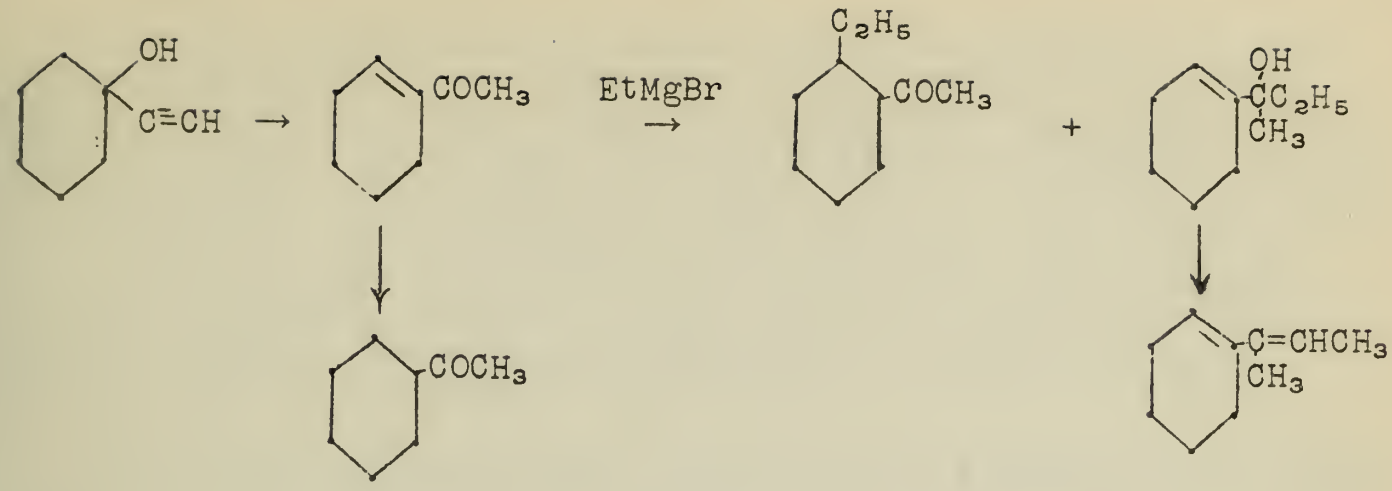


As an example, the rearrangement of 1-ethinyl-1-cyclohexanol was accomplished by heating with 8 to 9 parts of 86% formic acid for 2.5 hours at 103°C. The neutral fraction of the mixture yielded an unsaturated carbonyl compound, $C_8H_{12}O$, that gave a semicarbazone, an oxime and a phenylhydrazone. It was reduced by one mole of hydrogen to a compound, $C_8H_{14}O$, which gave a semicarbazone. It reacted with ethylmagnesium bromide to give two products each having the analysis $C_{10}H_{18}O$, one of which gave a semicarbazone and the other gave both a benzoate and an acetate. The acetate was treated with acetic anhydride and sodium acetate to give a hydrocarbon, $C_{10}H_{16}$.

Rupe concluded the structure of these compounds to be as follows.



Amore logical explanation, based on our present knowledge of 1,4 addition of the Grignard reagent, predicts the following.



Later work of Rupe on the rearrangement products of the acetylene carbinols from 3-methyl and 4-methylcyclohexanone proved the ketone structure, although he does not point out the contradiction in his earlier work. It has been shown in this laboratory that the rearrangement product of the acetylene carbinol from isohexyl methyl ketone is 3,7-dimethyl-3-octen-2-one instead of 3,7-dimethyl-2-octenal.

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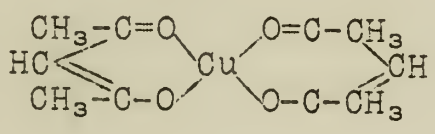
Reported by Herman I. Enos, Jr.
October 24, 1945

METALLIC DERIVATIVES OF 1,3-DIKETONES

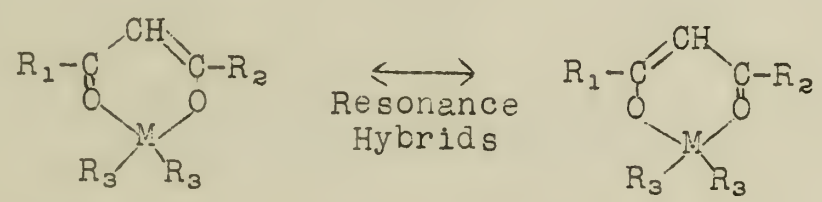
Metallic derivatives of 1,3-diketones (β-diketones), β-keto-esters, β-diesters, etc., have been recognized since the latter part of the 19th century. These compounds are of importance to the organic chemist because they afford a means of purification of the keto compounds. The alkali metal derivatives are important as they are extensively used in organic synthesis, i. e., the acetoacetic ester synthesis and the malonic ester synthesis. The metallic derivatives are all easily made by treating the ketones (which exist as tautomeric mixtures of enol and keto forms) with metallic salts or bases. The metal ions replace the enolic hydrogens giving rise to the metallic derivatives.

The isolated alkali metal derivatives of β-diketones are salt-like compounds, while the polyvalent metallic derivatives have the properties of truly covalent compounds. To account for this co-valent behavior a chelated structure (6) has been postulated by Werner (12) and later by Tschugaeff (11). This chelated structure has been proven to be the correct representation of these compounds (1, 2, 9), i. e., copper acetylacetonate has the formula:



A study of the effects of structural changes on metallic derivatives of this type is limited by the increase in complexity of these compounds as the primary valence of the central metal atom is increased.

Since the derivatives of thallium, dialkylthallium, trialkyl platinum, and dialkyl tellurium contain only one chelated ring, an extensive study of the effect of structural changes on these com-pounds has been made by Menzies (4, 5) and Morgan and coworkers (7, 8, 9). These compounds can all be represented by the following general formula:



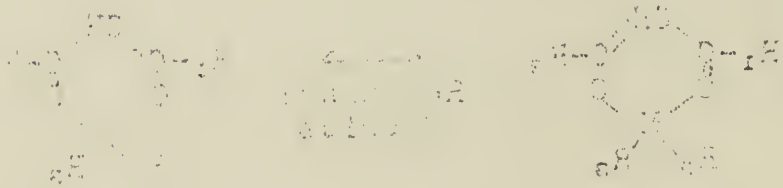
A study of structural changes and their effects on the melt-ing points of these metallic derivatives is given in Table I. This table shows that when the metal is alkylated at position R_3 there is a rise in the fusion temperature followed by a gradual decrease as the size of the alkyl group increases. An increase in size of groups R_1 or R_2 has a greater effect on the melting point than a corresponding change in position R_3. No thallium derivatives are formed if the median H atom on the diketone is replaced by an

HEXAMIC DERIVATIVES OF 1,3-DIKETONES

[illegible]

[illegible]

Some [illegible] of [illegible], [illegible], [illegible], platinum, and [illegible] [illegible] extensive study of the [illegible] [illegible] [illegible] (7, 8, 9). These compounds can all be [illegible] [illegible] general formula:



[illegible]

alkyl group. However, metallic derivatives of these substituted diketones are formed by metals other than thallium, the only exception being that no metallic derivatives are formed if the substituted group is branched at the α-carbon atom (as in the isopropyl group).

TABLE I

Melting Point Studies

	Compounds				Melting Points
	R_1	R_2	R_3	3	
1.	Me	Me	--	H	160.5°
2.	Me	Me	Me	H	213.5
3.	Me	Me	Et	H	200.0
4.	Me	Me	Pr	H	180.0
5.	Me	Me	Bu	H	137.5
6.	Me	Et	--	H	89.5
7.	Me	Et	Me	H	162.0
8.	Me	Me	Et	H	146.5
9.	Me	Et	Pr	H	108.0
10.	Me	Et	Bu	H	72.0
11.	Et	Et	--	H	70.0
12.	Et	Et	Me	H	120.0
13.	Et	Et	Et	H	115.5
14.	Et	Et	Pr	H	89.0
15.	Et	Et	Bu	H	41.0
16.	Me	Me	--	H	230.0 sublimes
17.	Me	Me	--	n-Pr	215.0
18.	Me	Me	--	iso-Pr	No. deriv. formed
19.	Me	Me	--	n-Bu	186.0
20.	Me	Et	--	Et	176.0
21.	Me	Et	--	n-Bu	156.0
22.	Me	Et	--	Cl	138.0
23.	Me	iso-Pr	--	H	168.0
24.	Me	Non	--	H	114.0
25.	Me	Oet	--	H	193.0

(Compounds 1-15 are thallium derivatives;
16-25 are copper derivatives)

Table II gives an indication of the volatility of these compounds in steam (3).

TABLE II

Volatility of Thallium Derivatives in Steam

Diketone	Tl	$TlMe_2$	$TlEt_2$	$TlPr_2$	$TlBu_2$
acetylacetone	-	-	-(A)	+(B)	+(C)
propionylacetone	-	-	-	M.P.	M.P.
dipropionylmethane	-	+(A)	M.P.(B)	M.P.(C)	M.P.

(-) = not steam distillable.
(+) = contained dialkylthallium ion but no solid complex came over.
M.P. = unchanged chelate cpd. came over in sufficient quantity for a melting point detn. A, B. C are isomeric pairs.

Solubility studies (Table III) show that changing R_3 from Me to Et causes an increase in solubility in n-hexane of about 1.7 times, while for a similar change in both R_1 and R_2 groups this solubility is increased about 120 times.

TABLE III

Solubilities of Thallium Derivatives in n-Hexane at 27°C (expressed in g. substance per 100 g. solvent)

Compound	Tl	$TlMe_2$	$TlEt_2$	$TlPr_2$	$TlBu_2$
acetylacetonate	0.012	0.12	0.15(A)	0.20(B)	1.32(C)
propionylacetonate	1.52	0.77	4.65	12.4	49.3
dipropionylmethane	41.1	14.5(A)	17.0(B)	21.7(C)	very sol.

The thallous compounds and many other of these metallic derivatives show an association of about two when in benzene solution. This association has been explained by Sidgwick (10) through the use of the effective atomic number concept. The most satisfactory explanation for the association of these compounds was given by Menzies (5) who explained it by means of dipole moments. When groups R_1 and R_2 are the same the association is small, when they are different the association is increased. Association is greatest for the metallic derivatives of β-ketoesters; methyl ester derivatives are less associated than ethyl ester derivatives.

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No general references for these compounds have been found. To find any specific metallic derivative look in Beilstein or Chemical Abstracts under the diketone in question.

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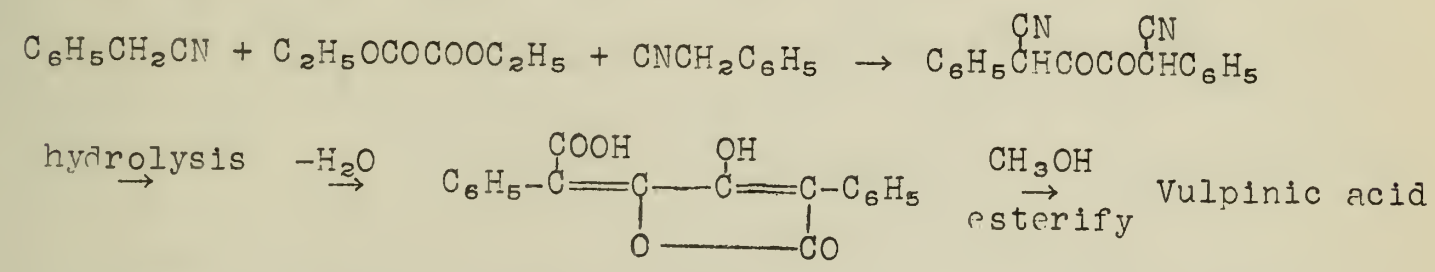
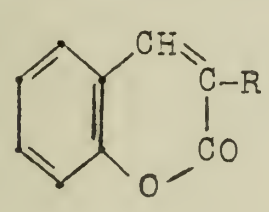
Reported by F. E. Boettner
October 31, 1945.

STRUCTURE AND TOXICITY OF SOME NEW SYNTHETIC INSECTICIDES

Recent progress made in the field of insecticides has been reported by Läuger, Martin, and Müller, chemists for J. R. Geigy Company, a Swiss dye firm. A few of the early effective compounds were the copper and lead arsenates, the alkaline-earth silicofluorides, and certain dyes. The particular interest of these chemists lay in various lactones produced by plants. Vulpinic acid, a yellow-colored insecticide occurring in various lichen and moss, was prepared synthetically and its activity was studied.



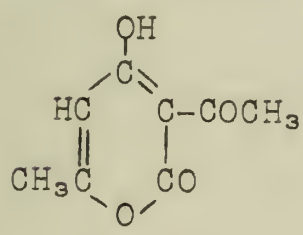
The plant world furnished two other compounds of important insecticidal activity, rotenone and pyrethrin, both of which are contact poisons. The structures of rotenone, pyrethrin, and vulpinic acid suggested a theory that the γ-lactone group was responsible for the toxicity, so a series of coumarin derivatives was prepared.



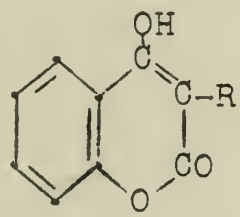
R: Cl, $CO_2C_2H_5$, C_6H_5 (low toxicity)

R: C_2H_5, C_4H_9, $COCH_3$ (medium toxicity)

Next dehydroacetic acid was submitted to toxicity tests and showed very good activity; consequently, certain coumarins which may be considered benzologs of dehydroacetic acid were prepared.

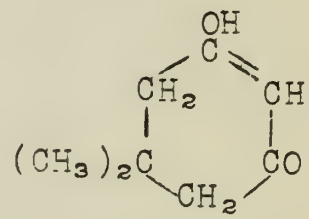


dehydroacetic acid (active)



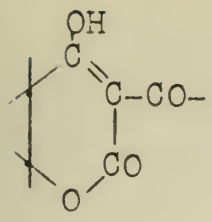
R: $COCH_3$, $CO_2C_2H_5$ (very active)

R: H(benzotetronic acid) (inactive)

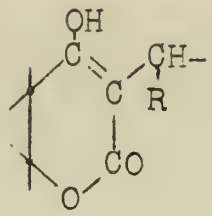


dimethyldihydroresorcinol (inactive)

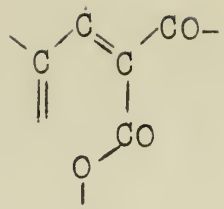
With these compounds in mind the assumption was made that atomic arrangement I was necessary for insecticidal activity. At first it was not expected that benzotetronic acid would possess no insecticidal activity. Nevertheless, when benzotetronic acid was allowed to condense with benzaldehyde and dimethyldihydroresorcinol with formaldehyde, active compounds were obtained.



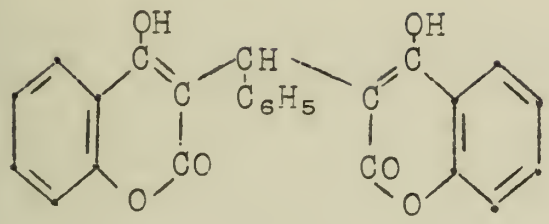
I

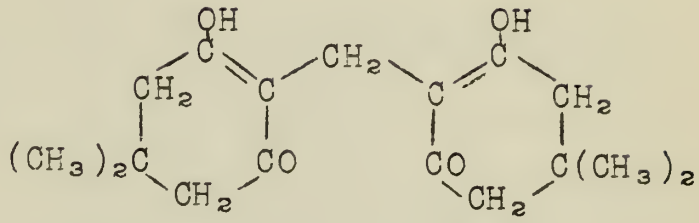


II

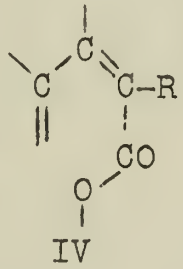


III



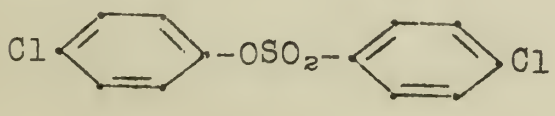


Atomic arrangement I was complemented with atomic arrangement II. However, when the lactone ring of the coumarin series was opened with the formation of certain esters, it was found that the toxicity had not been reduced. This led to atomic arrangement III along with I and II. As a result a composite arrangement IV was made.



IV

But all these active compounds shown are useless as permanent moth-proofing agents since their activities, like that of rotenone and pyrethrin, are destroyed upon exposure to light. There followed a period in which innumerable compounds were tested. A lead was obtained when Polar Red, a dye, was found to be effective against moths. But the treatment of moths with the completely purified dye had no effect. It was then assumed that a trace of the phenolic ester of p-toluenesulfonic acid was the toxic ingredient. From this information a whole series of aromatic sulfonic esters was prepared. However, the only compound observed to have high toxicity was p-chlorophenyl p-chlorobenzenesulfonate.



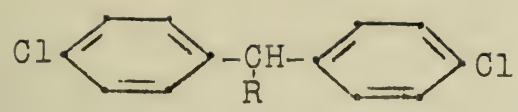
(In this series chlorine atoms and methyl groups were used in almost every conceivable position on the benzene rings.)

The activity of the above compound reminded the chemists that from an earlier unrelated experiment they were in possession of p,p'-dichlorodiphenyl sulfone, $ClC_6H_4SO_2C_6H_4Cl$. As a stomach poison it revealed an activity never before encountered. Therefore, sulfones and their related compounds were prepared for biological testing.

Highly Active	Inactive
4,4'-dichlorodiphenyl sulfone	3,3'-dichlorodiphenyl sulfone
3,4,4'-trichlorodiphenylsulfone	3,3',4,4'-tetrachlorodiphenyl sulfone
2,4,4'-trichlorodiphenylsulfone	3,4-dichlorodiphenyl sulfone
4,4'-dichlorodiphenyl sulfoxide	diphenyl sulfone
4,4'-dibromodiphenyl sulfoxide	4,4'-dihydroxydiphenyl sulfone
4,4'-dichlorodiphenyl sulfide	4,4'-dichlorodiphenyl methane
4,4'-dichlorodiphenyl ether	4,4'-dichlorobenzophenone

These results led them to suspect that p,p'-dihalogenated binuclear benzene derivatives must be present for high toxicity. It was at this stage of the research on insecticides that Dr. Paul Müller submitted DDT (a compound prepared many years before but not used in the dye industry because of its unreactivity) for testing on flies. DDT was shown to be successful and, according to the authors, DDT was the first synthetic compound ever to possess such high toxicity and to be both a contact poison and a stomach poison.

On the assumption that DDT initially exerts its effect on the nervous system, the following compounds were compared: chlorobenzene, p-dichlorobenzene, o-dichlorobenzene, 4,4'-dichlorodiphenyl sulfone, and DDT. Chlorobenzene is a respiratory poison and still more effective are the dichlorobenzenes. 4,4'-Dichlorodiphenyl sulfone has been conceived as a nonvolatile condensed chlorobenzene system held together by the electronegative sulfonyl group. DDT contains a similar system but with a chloroform nucleus attached to the molecule. Since chloroform dissolves readily in nerve lipids, a number of new insecticides were prepared containing the residues of other respiratory anesthetics in the toxic chlorobenzene system. These were highly toxic but, because of certain characteristics of the compounds, preparation on a commercial scale was hardly feasible.



$ClC_6H_4-CH-CH-C_6H_4Cl$
$\quad\quad CH_2(O)$

$ClC_6H_4-CH-O-CH-C_6H_4Cl$
$\quad\quad CH_3 \quad CH_3$

$ClC_6H_4-C-O-C-C_6H_4Cl$
$\quad\quad CH_2 \quad CH_2$

respiratory anesthetics

$CHCl_3$
$CHBr_3$
CH_2Cl_2
CH_3Cl
$Cl_2C{=}CHCl$
CH_3NO_2
$CH{\equiv}CH$
$CH_2{=}CH_2$
cyclopropane, ethylene oxide, diethyl ether, and divinyl ether

The following generalization was made for a highly active insecticide: the toxic component must possess a group which guarantees a very pronounced lipoid solubility.

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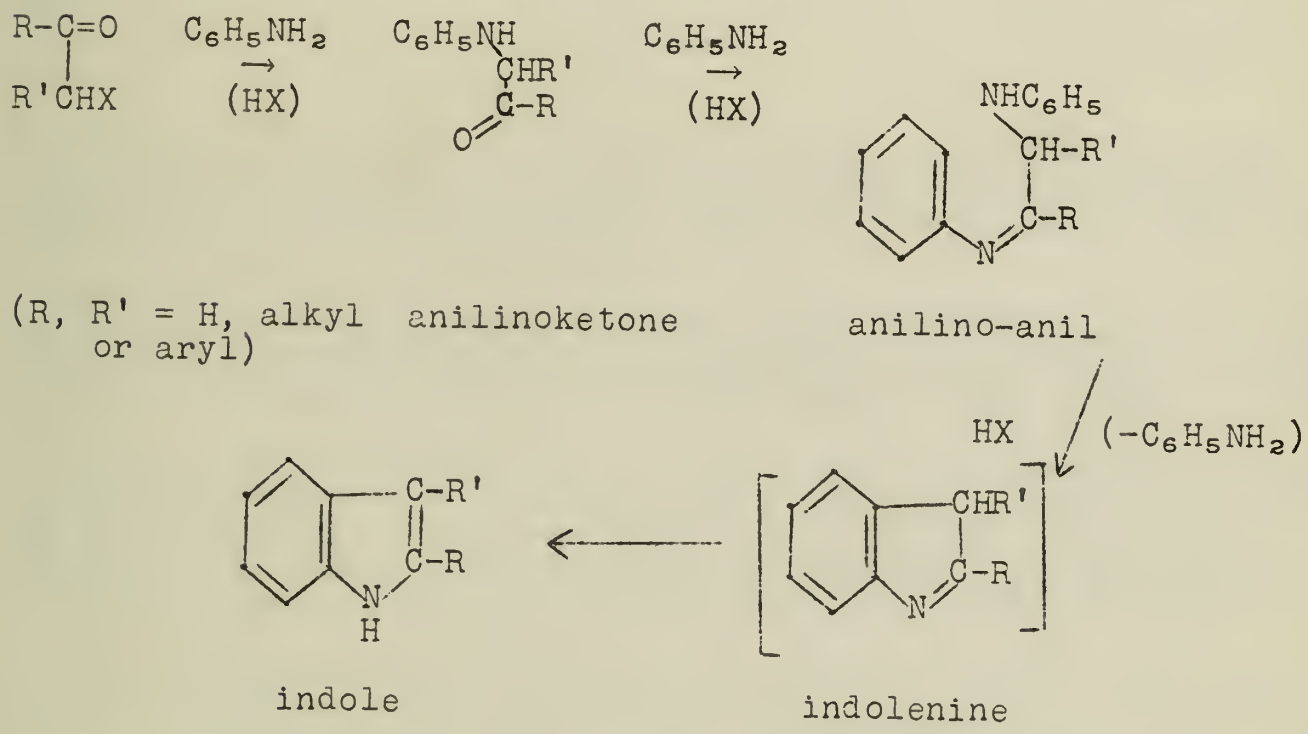
Reported by D. B. Guthrie
October 31, 1945

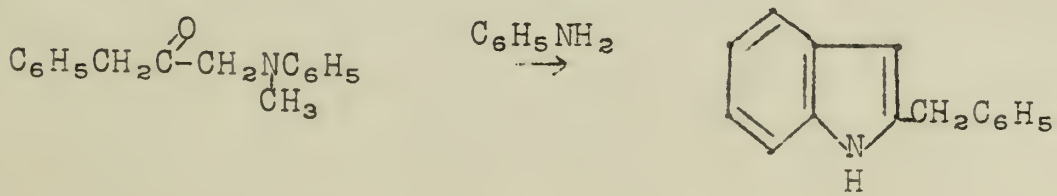
THE BISCHLER MECHANISM OF INDOLE FORMATION FROM α-BROMOKETONES

The mechanism of the formation of indoles when an α-halogenated ketone is heated with an arylamine has been the subject of numerous investigations. In 1892 Bischler postulated the following mechanism consisting of three steps.

1. Replacement of the α-halogen by the arylamino group.
2. Reaction of the second mole of amine with the arylamino ketone to form an "anilino-anil".
3. Elimination of the "first" molecule of the arylamine to form presumably, the indolenine which rearranges into the stable indole modification.



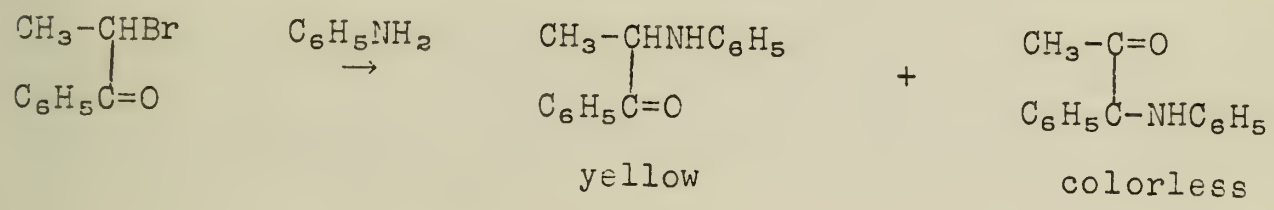
This hypothesis stood unchallenged until 1933, when Julian and Pikl found that in the preparation of 2-benzyl indole



they always obtained in varying yields another product which was identified as N-methyl-3-benzylindole. The isolation of the latter product indicates it is not necessarily true that the first amino group entering the reaction is the one that is eliminated.

Recently Julian and his coworkers have published a lengthy and critical discussion of the Bischler mechanism as the result of more than ten years of investigation. They consider each step of the mechanism in the order in which they occur.

Step 1. Formation of Arylamino Ketone.--The reaction of aniline with an α-bromo ketone is not always a simple substitution reaction. Alpha-bromopropiophenone gives two products on treatment with aniline.



Furthermore, starting with either the pure yellow or the pure colorless isomer and heating in the presence of equivalent amounts of aniline hydrobromide each pure compound was converted into a mixture of both isomers.

Similar results were obtained using α-bromo-β-phenylpropiophenone. Interconversion of the isomeric anilino ketones could be accomplished by heating with hydrochloric acid alone.

These observations indicate that the reaction is not entirely a simple displacement. Julian points out that the reaction may involve addition of the arylamine to the carbonyl group and subsequent elimination of hydrogen halide and that the initially formed anilino ketone may itself rearrange into its isomer.

Although at present there is no direct evidence that Step 1 involves addition, the possibility of isomerization of the anilino ketone has definitely been established. Hence, the first step of the Bischler mechanism, if correct, must be modified to include the possibility of rearrangement of the originally formed anilino ketone.

Step 2. The Intermediate Anilino-Anils.--It is reasonable to assume that α-bromopropiomesitylene, due to steric hindrance, would fail to give both isomers when treated with aniline. In addition, steric effects would prevent addition of the second molecule of amine to the carbonyl group, thus preventing indole formation. Actually this has been observed in the laboratory. Treatment of the bromo ketone yielded only the α-anilino ketone, which on further treatment with aniline, failed to give any indole.

A study of desylaniline has given additional evidence in support of the intermediate "anilino-anil" hypothesis. Desylaniline when heated several hours with one molecule of aniline in the presence of hydrogen chloride gave excellent yields of 2,3-di-

phenyl indole. Substituting dimethylaniline for aniline in this reaction resulted in a practically quantitative recovery of the desylaniline. It is logical to assume that if the formation of the indole proceeded by a direct ring closure, dimethylaniline would produce the same result as aniline itself.

Conclusive evidence in support of the second step came from the isolation of desylaniline anil from the reaction of desylaniline and aniline. This anil could be converted to 2,3-diphenylindole by treatment with aniline and hydrochloric acid.

Step 3. Elimination of the Arylamine.--It has been shown by Garry that true "anilino-anils" actually give indolenines when heated in the presence of hydrochloric acid. However, the intermediate formation of indolenines is not absolutely essential to the Bischler mechanism.

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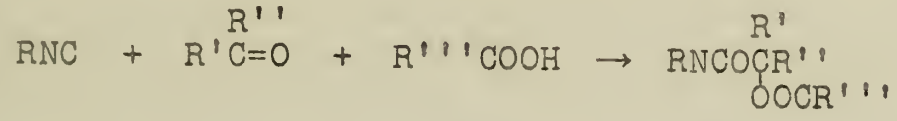
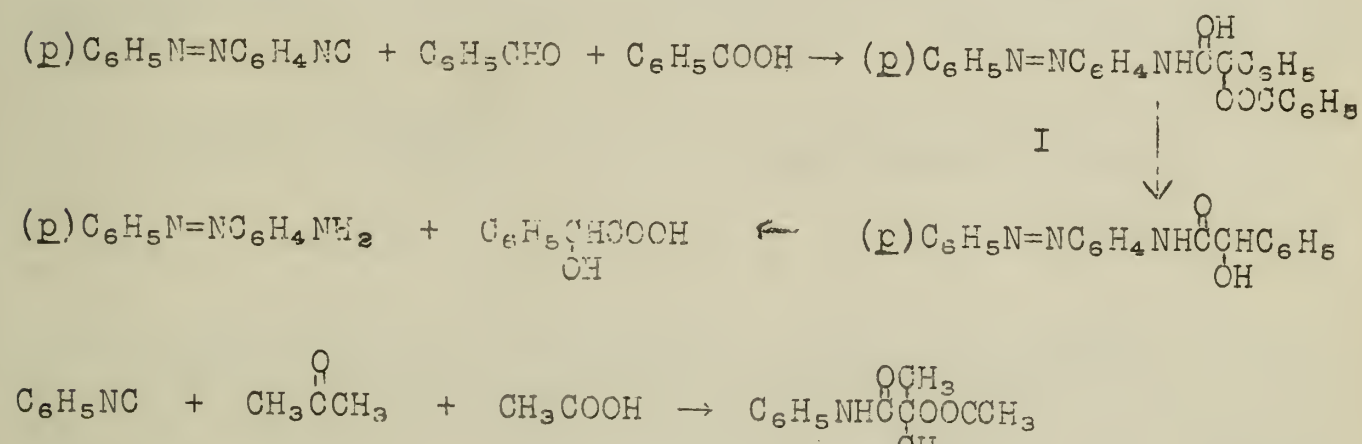
Reported by B. H. Velzen
November 7, 1945.

THE PASSERINI REACTION

An interesting reaction of isonitriles with carbonyl compounds and organic acids has been reported by Passerini in a long series of articles.

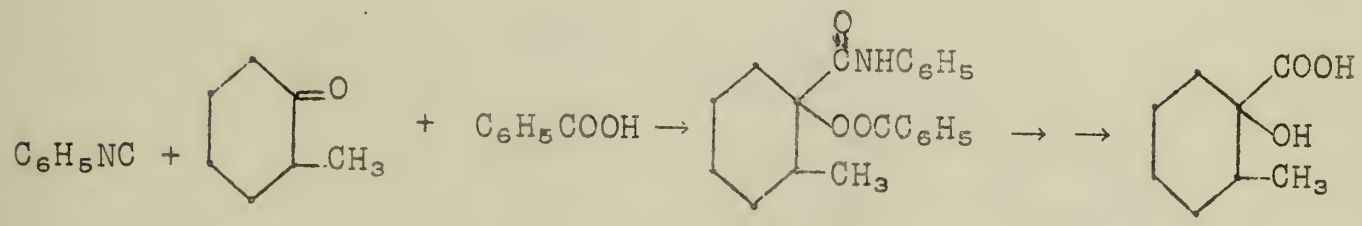


Phenyl isocyanide or p-azobenzeneisocyanide were used in most of the investigations although it was shown that an aliphatic isonitrile such as propyl isocyanide could be utilized. Various aldehydes and ketones were used. Acetone, methyl ethyl ketone, cyclohexanones, acetaldehyde, benzaldehyde, and piperonal reacted in the above manner with an isocyanide and an organic acid. In the normal type of reaction either benzoic acid or acetic acid was used. The nature of the products obtained can be seen from the reactions of acetaldehyde, acetone, and methylcyclohexanone.



I

II



III

Passerini was very interested in demonstrating the presence of the hypothetical intermediate IV which might originate by the interaction of the carbonyl compound and the organic acid.

$$R_2CO + R'CCOH \rightarrow R_2\underset{OH}{C}OOCR'$$

IV

IV would correspond to a bisulfite or cyanohydrin addition product. Support for this intermediate was found in the fact that α-hydroxyamides of the type produced in the reaction are acetylated or benzoylated with great difficulty and would probably not form under the experimental conditions used, were the hydroxyamide produced as the initial product. Good evidence for this intermediate was obtained also by a study of the reaction between the hydrated aldehydes, chloral hydrate or butyl chloral hydrate, and phenylisocyanide. The reaction proceeded normally in these cases.

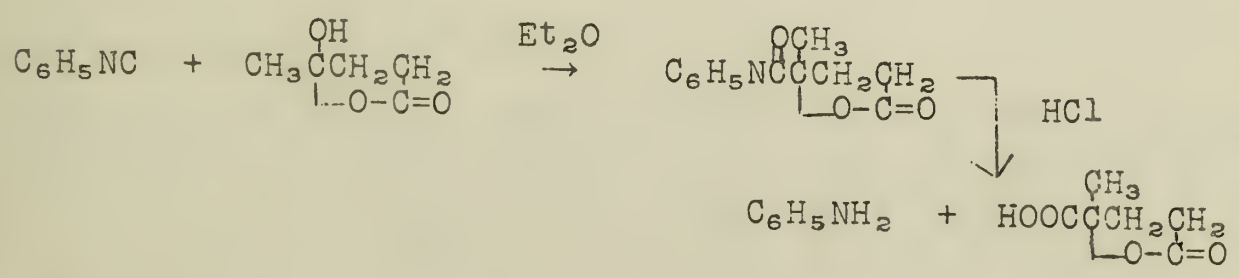
$$C_6H_5NC + Cl_3CCH(OH)_2 \rightarrow C_6H_5NHCO\underset{OH}{C}HCCl_3$$

The simple reaction of isonitriles with organic or mineral acids led to the formation of substituted formamidines and carbon monoxide.

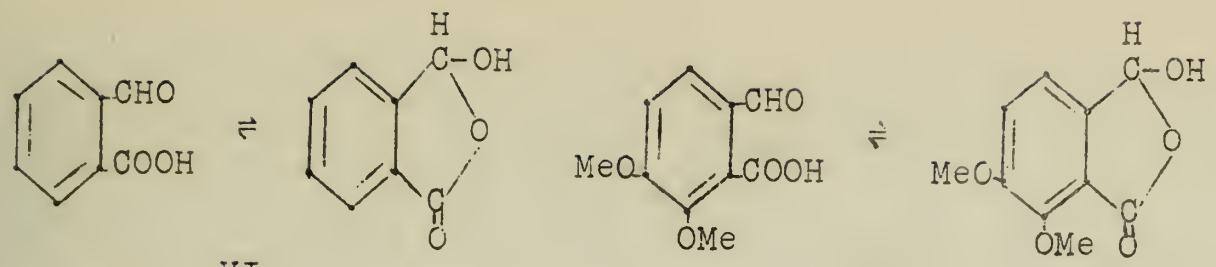
$$2\ ArNC + RCOOH + H_2O \rightarrow ArN{=}CHNHAr\cdot 2\ RCOOH + CO$$

V

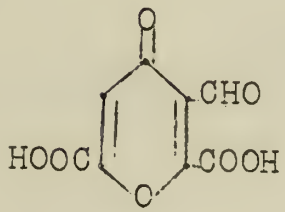
In the case of acetic acid ($R{=}CH_3$), V was very soluble whereas acids such as mandelic, lactic, or salicylic produced association compounds which were readily isolated. In support of the proposal of an intermediate such as IV, it was observed that levulinic acid gave a normal reaction product indicating that this acid reacted in the lactone form.



Similarly phthaldehydic (VI) and opianic (VII) acids gave typical reaction products indicating a lactone type structure. Meconic acid (VIII) on the other hand yielded formamidine derivatives.



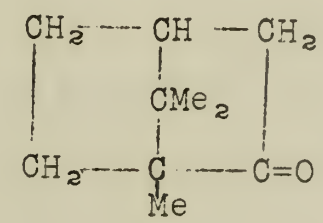
VI VIII



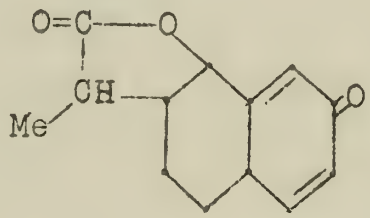
VIII

Additional data was obtained to show the presence of the "hydrated" carbonyl intermediate (IV) from melting points, conductivity, and change in optical rotation of mixtures of carbonyl compounds and organic acids.

Recently an attempt has been made to apply the Passerini reaction to sterols in an effort to build up oxygenated side chains on the sterol nucleus and this work has led to a coordination of the failures of the reaction thus far observed. No reaction had been observed by Passerini with camphor (IX) and santonin (X).

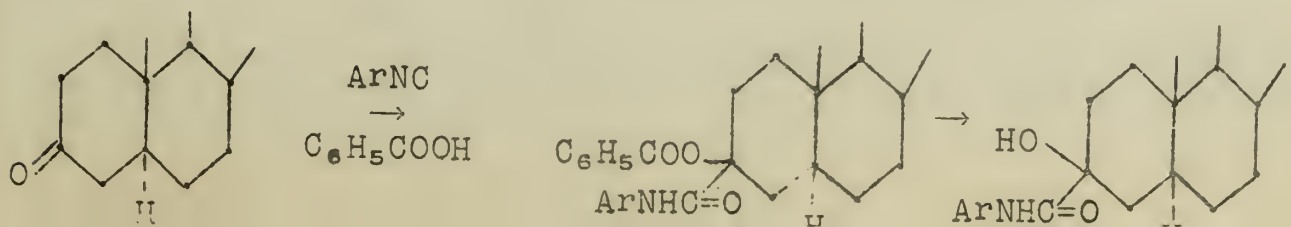


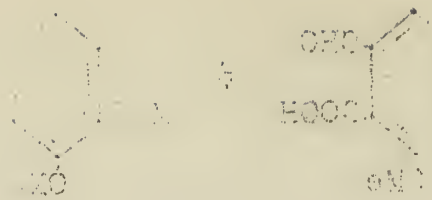
IX



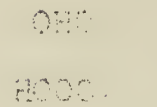
X

Baker and Schlesinger could not apply the reaction to dehydroandrosterone, similarly substituted to IX, and ascribed the difficulty to blocking effects of the substituents. It was also observed that α,β-unsaturated ketones in general did not react. To X as the lone example of this type of failure was added crotonaldehyde, benzalacetophenone, and cholestenone. However, the analogous saturated steroid, 3-cholestanone, was successfully used.





VIII



VIII

[illegible] to show the presence of the [illegible] (IV) from melting point, optical rotation of mixtures of [illegible] and [illegible].

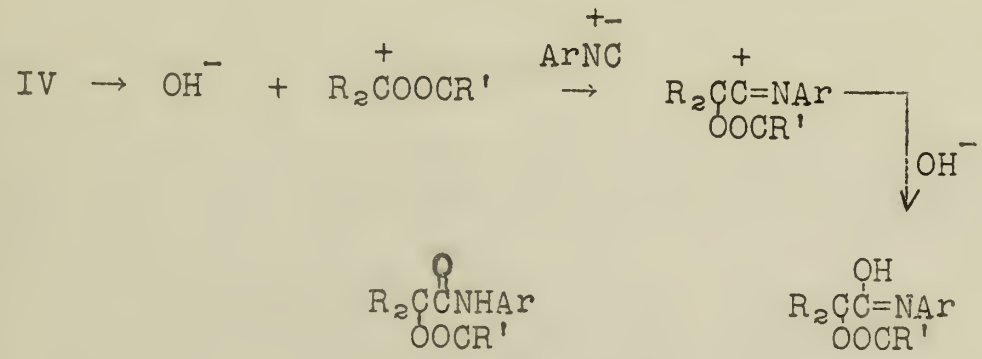
[illegible] been made to apply the Baeyer-Villiger [illegible] to build up oxygenated side [illegible] and this work was led to a coordinate [illegible] reaction thus far observed. No [illegible] by Baeyer-Villiger with camphor (IX) and

X

IX

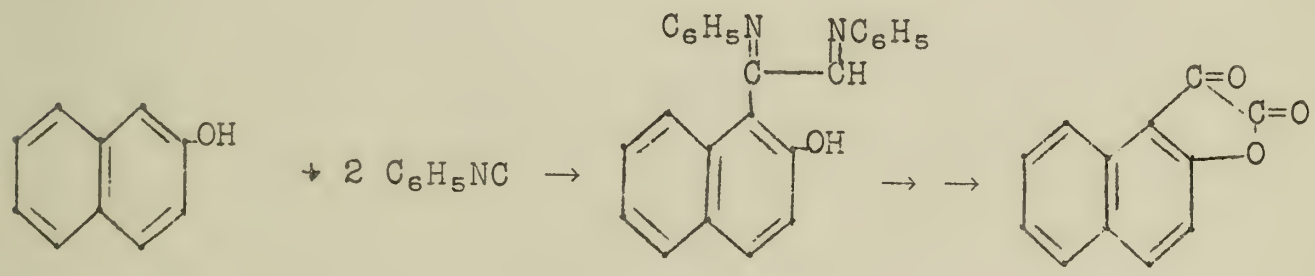
[illegible] could not apply the [illegible] tion to dehydrocitronellic [illegible] to IX, and [illegible] the [illegible] effects of the substituents. It was also [illegible] unsaturated acids in general did not react. [illegible] example of this type of failure was added crotonophenone, and oleic acid. However, the [illegible] acid, 3-oleic acid, was successfully

These latter investigators suggested a scheme for the reaction which ignored the large amount of evidence which Passerini had produced for the intermediate "hydrated" carbonyl group. By a modification of their suggestion, the course of the reaction may be represented as an attack at the nucleophylic center. The failure of unsaturated carbonyls to undergo the reaction may then be explained by a certain amount of neutralization of the electrophylic center.

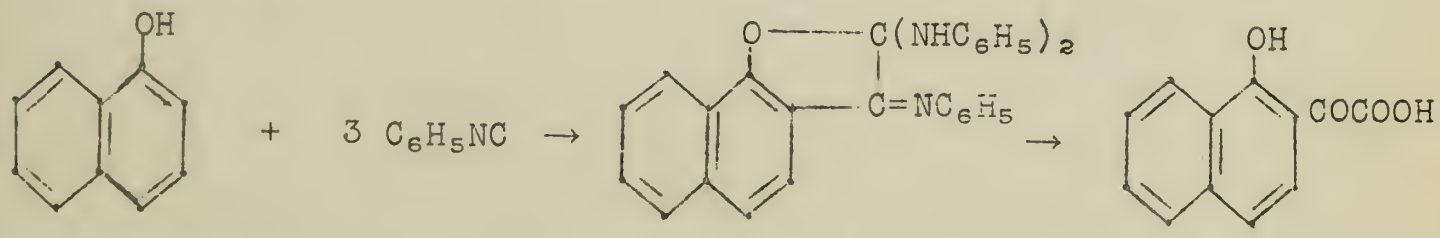


However, the use of other isonitriles with stronger nucleophylic centers did not force the reaction with α,β-unsaturated ketones.

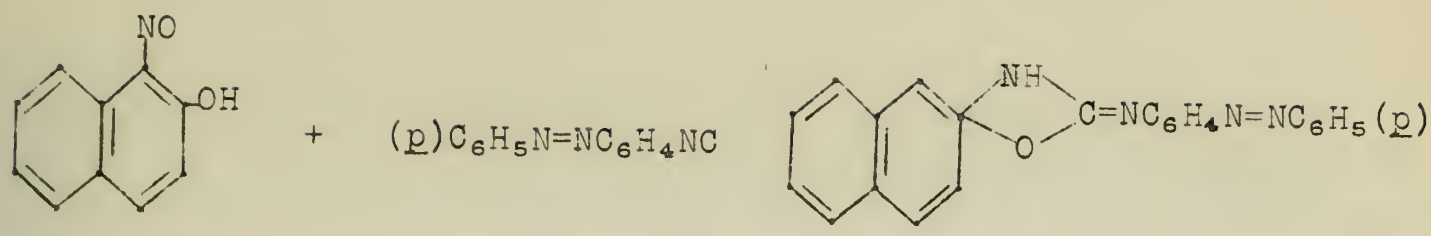
Passerini also applied the reaction to β-naphthols. The attack of the isonitrile group apparently occurred at the α-position and, instead of a subsequent addition of the hydroxyl group as before, one additional mole of isonitrile added.



Phenol was used in an identical series of reactions. α-Naphthol reacted with three moles of the isonitrile.



The final application of the reaction was to nitroso compounds such as α-nitroso-β-naphthol, nitrosobenzene, pernitrosomenthol, and pernitrosocamphor.



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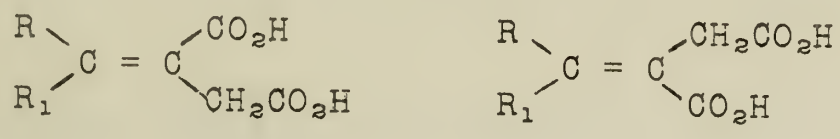
Reported by R. H. Reitsema
November 7, 1945

THE STOBBE CONDENSATION AND A RECENT MODIFICATION

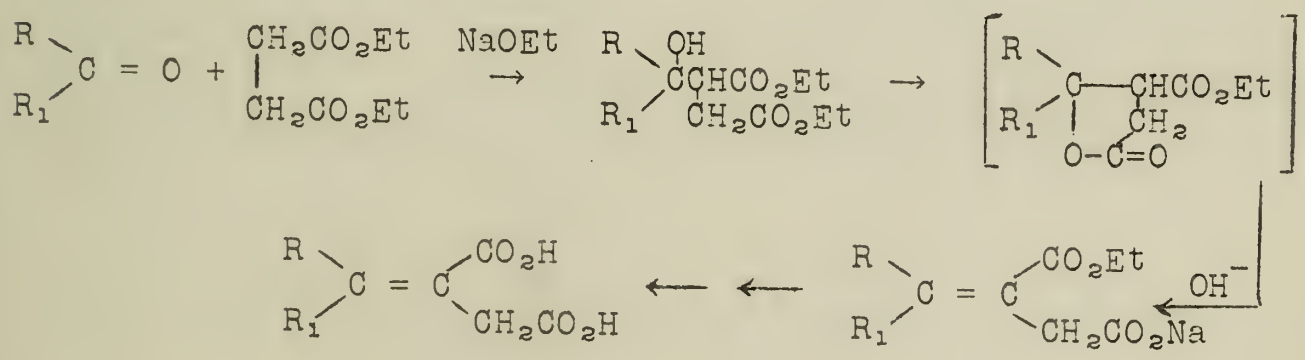
In 1894 Hans Stobbe submitted the first of a series of papers in which he described an alkoxide-catalyzed reaction between acetone and diethyl succinate to form an unsaturated dibasic acid. He extended the reaction to other aliphatic and aromatic ketones and postulated that substituted itaconic acids were formed.



It is evident that <u>cis-trans</u> isomerism will result and, when R and R_1 were unlike, Stobbe isolated two isomers. He described successful procedures for the condensations of diethyl succinate with ethyl methyl ketone, acetophenone, benzophenone, and acetone.

From analyses, he concluded that one mole of ketone reacted. The dicarboxylic nature was determined by gravimetric metal determinations and titration. The double bond was indicated by the ease of halogen addition and the fact that it was a β,γ carbon-to-carbon unsaturation by the observation that the dibromo compound yielded a monobromolactone spontaneously. This monobromolactone was then reduced to give a bromine-free lactone, identical with that derived from the original acid.

On the basis of the above evidence the following reaction mechanism was postulated.



Stobbe also described a procedure whereby he condensed benzaldehyde and diethyl succinate to give a good yield of phenylitaconic acid and its isomer.

In later papers he improved the procedure and investigated more fully some of the side products formed. From the acetophenone reaction he isolated three compounds, two of which were the <u>cis-trans</u> isomers, and a third which melted without decomposition, contrary to the behavior of the <u>cis-trans</u> compounds. With benzophenone he isolated only one compound and thus was led to the conclusion that the structure of the ketone dictated the number of products formed. He then studied dibenzyl ketone and desoxybenzoin

[illegible] AND A RECENT CONTRIBUTION

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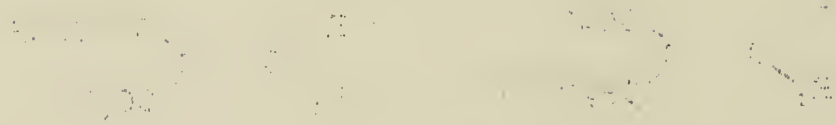

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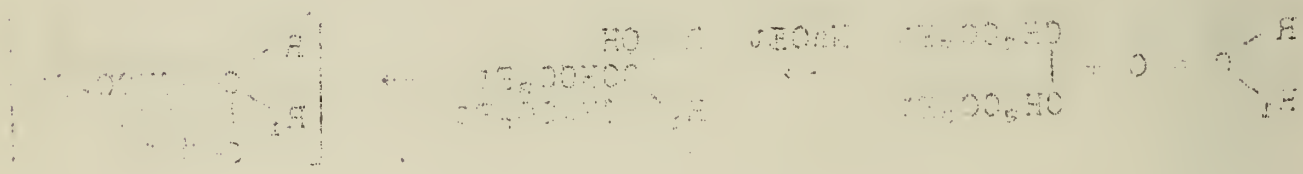
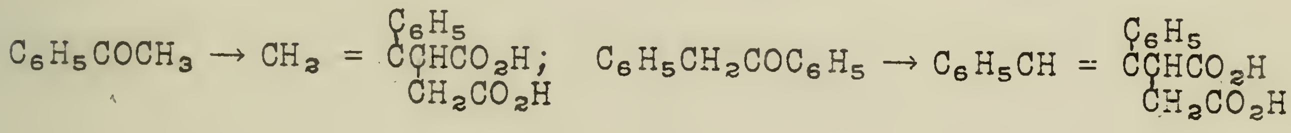


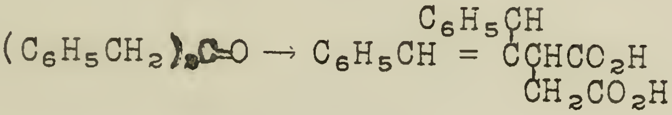
[illegible]

[illegible]

and in each case isolated a compound which behaved in a similar manner to the compound isolated from acetophenone. Oxidation of the compound from desoxybenzoin gave benzoic acid and β-benzoyl propionic acid. He also observed that formation of the anhydride from the resulting dicarboxylic acid was difficult and at times impossible. On this evidence he postulated that whenever the carbonyl of the ketone was flanked by a methylene group, derivitives of pyrotartaric acid would result. Thus:



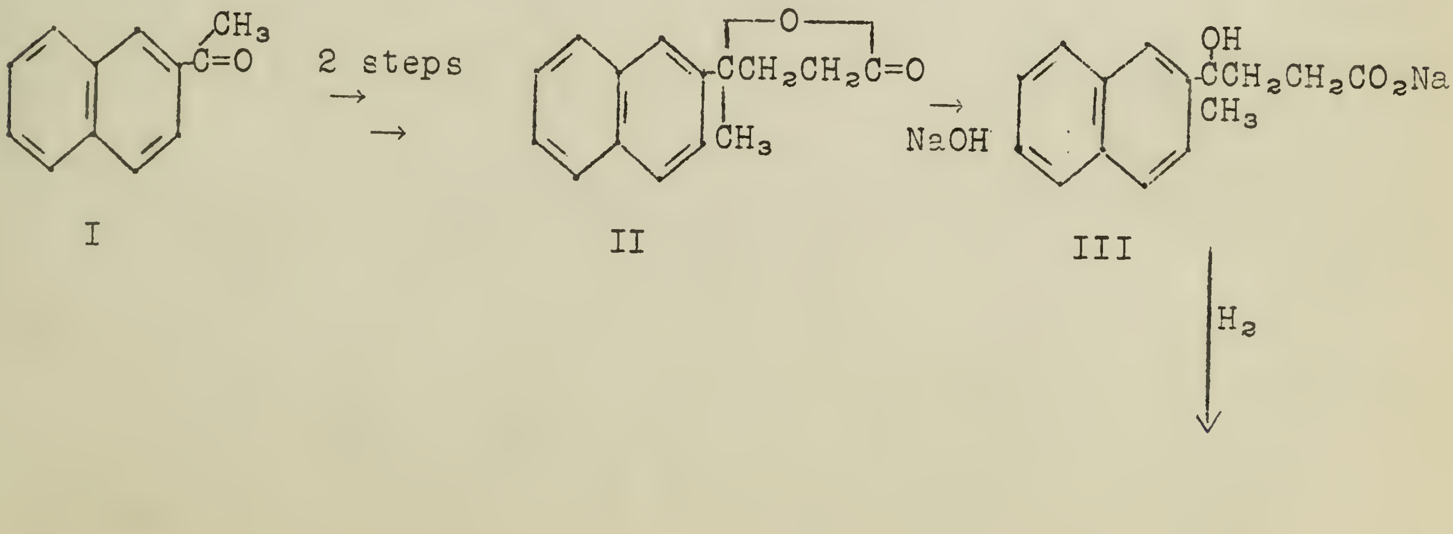
$$C_6H_5COCH_3 \rightarrow CH_2 = \overset{C_6H_5}{C}\underset{CH_2CO_2H}{C}HCO_2H; \quad C_6H_5CH_2COC_6H_5 \rightarrow C_6H_5CH = \overset{C_6H_5}{C}\underset{CH_2CO_2H}{C}HCO_2H$$



$$(C_6H_5CH_2)_2C{=}O \rightarrow C_6H_5CH = \overset{C_6H_5CH}{C}\underset{CH_2CO_2H}{C}HCO_2H$$

Inasmuch as all the above methylene groups were attached to aromatic rings Stobbe investigated propiophenone where the methylene was in an aliphatic chain. A considerable proportion of γ-ethylidene-γ-phenylpyrotartaric acid was formed.

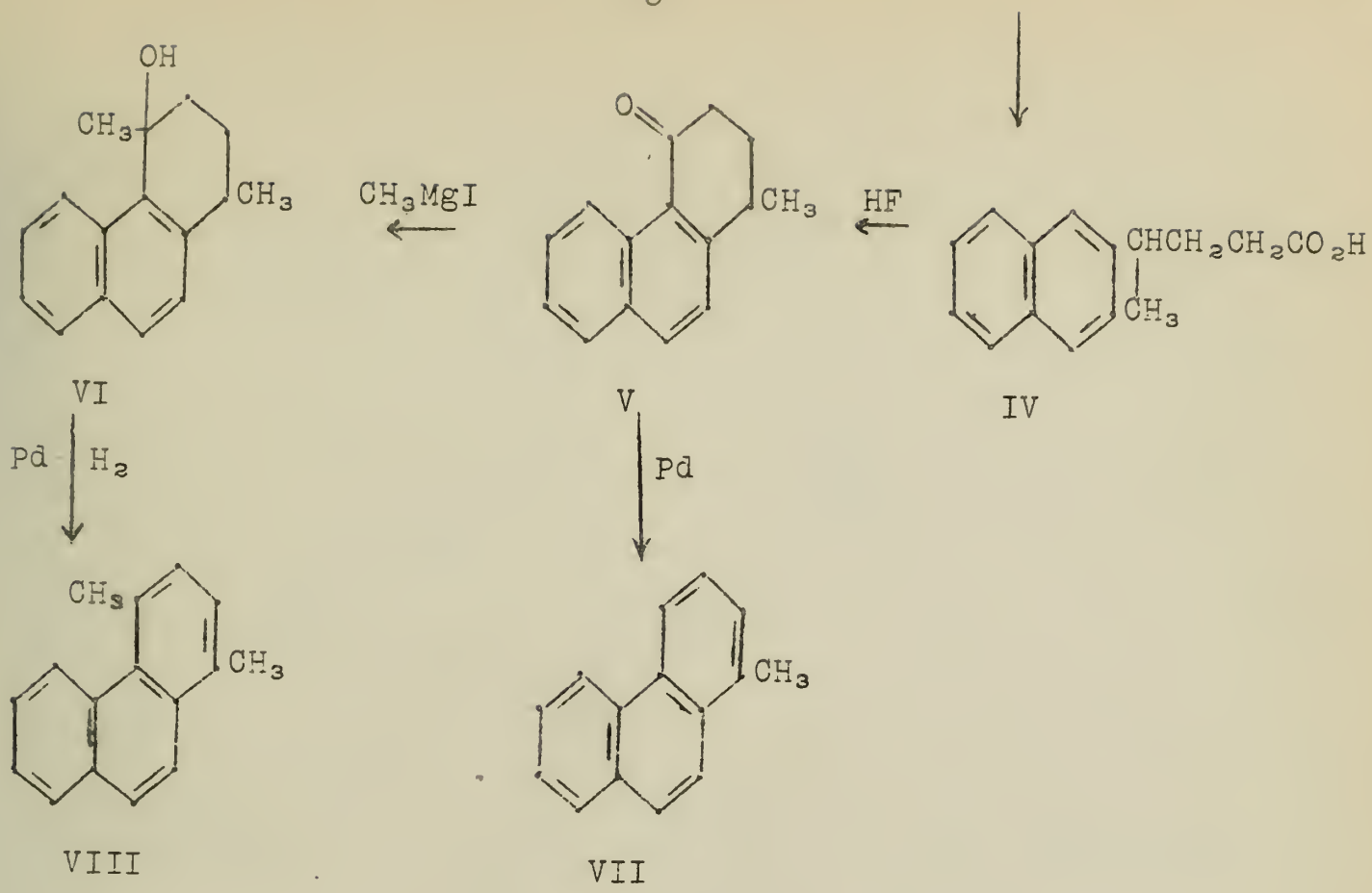
Recently Johnson, Goldman and Schneider extended the reaction to ketones of the naphthalene series and introduced the use of potassium tertiary butoxide as a condensing agent. They also made use of an acid-catalyzed decarbethoxylation of the half ester or lactone to introduce the propionic acid residue at the site of the carbonyl group of the ketone. They used acetyl naphthalene and followed Stobbe's procedure, using sodium ethoxide and potassium tertiary butoxide. The yields were 57-69% and 82% respectively. In addition the reaction time was cut to forty minutes. In accordance with the flow sheet, the polycyclic compounds VII was prepared.



I

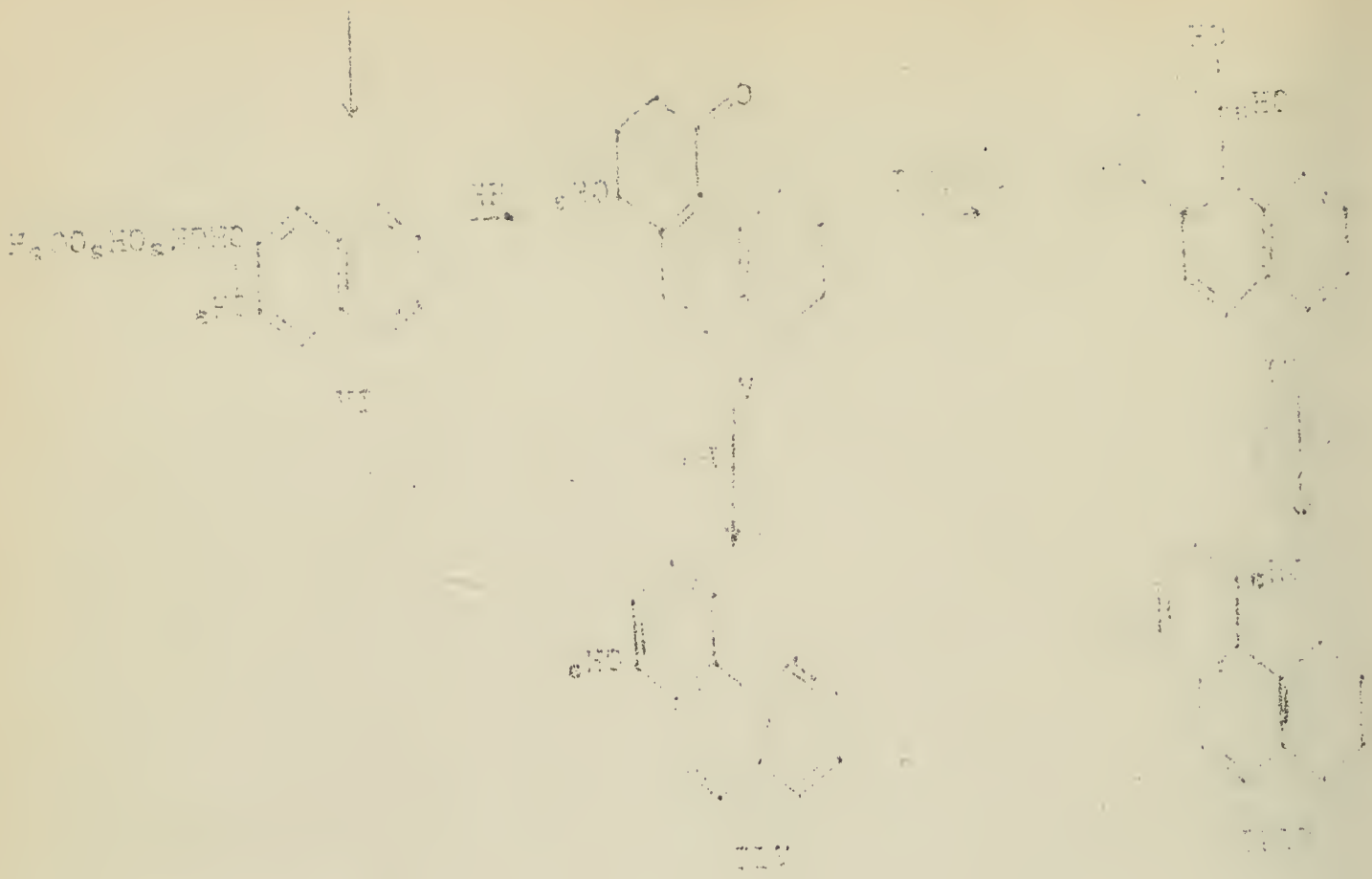
II

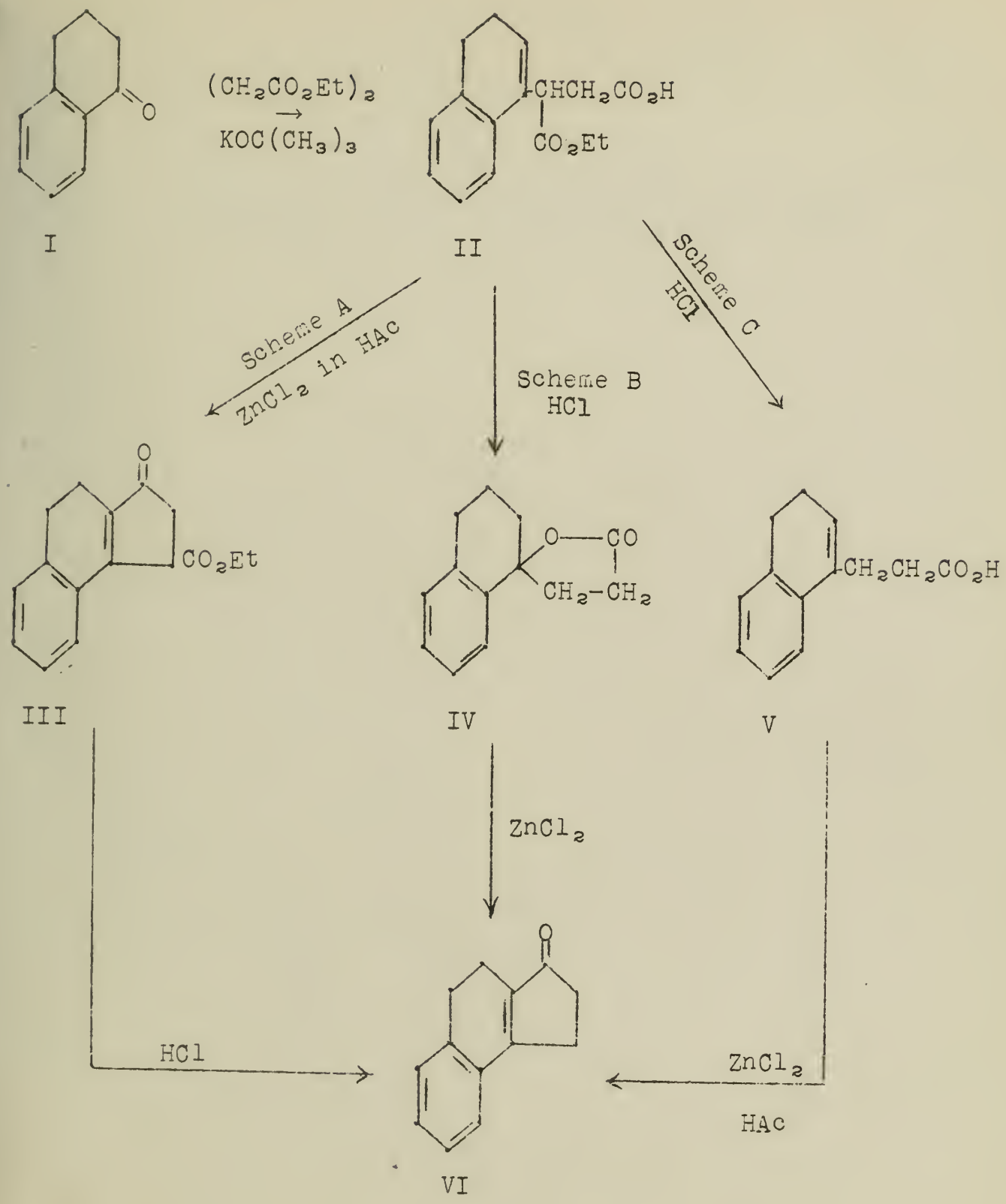
III



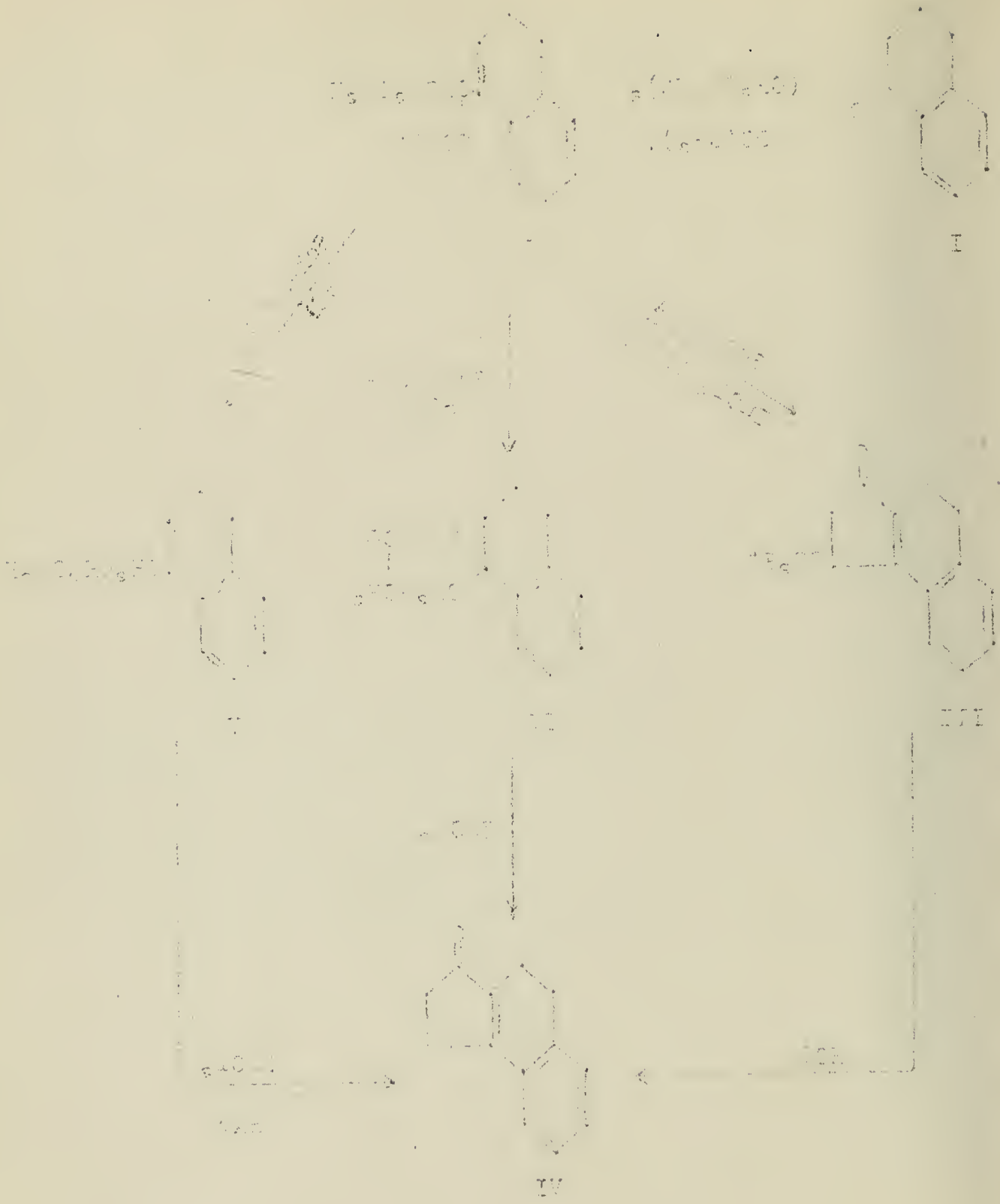
This modified Stobbe condensation appears applicable to the synthesis of lactones (II) from aryl ketones like I, and promises to be a general method of synthesizing polycyclic compounds which heretofore have been difficult to obtain because the initial γ,γ-disubstituted butyric acids were difficult to prepare.

Johnson was also interested in the general applicability of the Stobbe reaction to build up the cyclopentanone fused ring structure characteristic of the structure found in many sex hormones. In this respect he used tetralone-1 and carried out the following series of reactions.





Starting with 1-keto-1,2,3,4-tetrahydrophenanthrene, an analogous series of reactions can be effected. This series serves as a model for projected synthesis of true hormone structures starting with properly substituted derivatives of the 1-keto-1,2,3,4-tetrahydrophenanthrene.



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Reported by Leon Katz
November 14, 1945

RECENT DEVELOPMENTS IN ACETYLENE CHEMISTRY

German developments in acetylene chemistry were made with the use of four main catalysts; alkali alcoholates, zinc or cadmium salts of organic acids, copper or silver acetylides, and nickel carbonyl, $Ni(CO)_4$, combined with the discovery of the precautions necessary to work with acetylene under heat and pressure.

A. Vinylation.

1. Vinyl ethers.--No suitable industrial preparation of this class of compounds existed as late as 1940. Wislicenus (1) reported that methyl vinyl ether can be obtained from chloracetal and sodium at 140°. A German patent (2) describes a synthesis using acetylene and sulfuric acid under pressure at 0°, and treating the intermediate formed with an alcohol. However, under the conditions described, the vinyl ethers formed would undoubtedly resinify immediately.

Another method described in German patent 550,403 uses a vinyl halide and an alcoholate to secure the vinyl ether. This must have been the forerunner of the direct vinylation using acetylene and alcoholates under pressure. The patent (3) for this reaction describes the method by which acetylene and alcohol combine in the presence of about 1% alkali metal dissolved in the alcohol. Also listed as catalysts are strong alkalies and alkali cyanides. Apparently the mechanism is as follows.

$$C_2H_5OH + K \rightarrow C_2H_5OK + HC{\equiv}CH \rightarrow \begin{array}{l} C_2H_5O\text{-}CH{=}CH\cdot K \\ \qquad\qquad\qquad\qquad H\cdot OC_2H_5 \end{array}$$

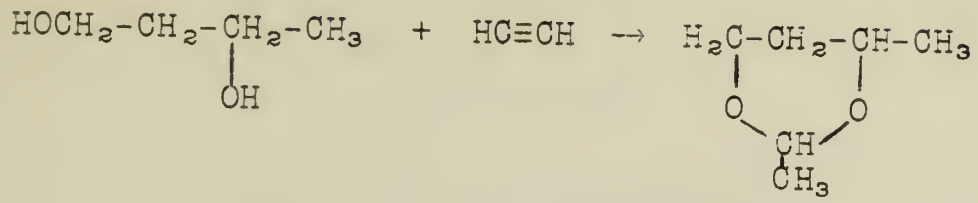
The alcoholate splits out and is again available for the reaction. Apparently this vinylation reaction is, with few exceptions, applicable to all organic compounds containing a hydroxyl group. An I. G. patent (4) lists compounds such as aliphatic, aromatic, hydroaromatic, and heterocyclic hydroxy compounds along with cyclohexanol, ring homologs such as decahydronaphthols, phenols, and napthols as specific examples for which this reaction has been used.

In the vinylation of glycols, both mono- and divinyl ethers are obtainable under suitable conditions.

$$\begin{array}{l} CH_2\text{-}OH \\ | \\ CH_2\text{-}OH \end{array} + HC{\equiv}CH \rightarrow \begin{array}{l} CH_2\text{-}O\text{-}CH{=}CH_2 \\ | \\ CH_2\text{-}OH \end{array} \rightarrow \begin{array}{l} CH_2\text{-}O \\ | \qquad\quad CH\text{-}CH_3 \\ CH_2\text{-}O \end{array}$$

$$\searrow \begin{array}{l} CH_2\text{-}O\text{-}CH{=}CH_2 \\ | \\ CH_2\text{-}O\text{-}CH{=}CH_2 \end{array}$$

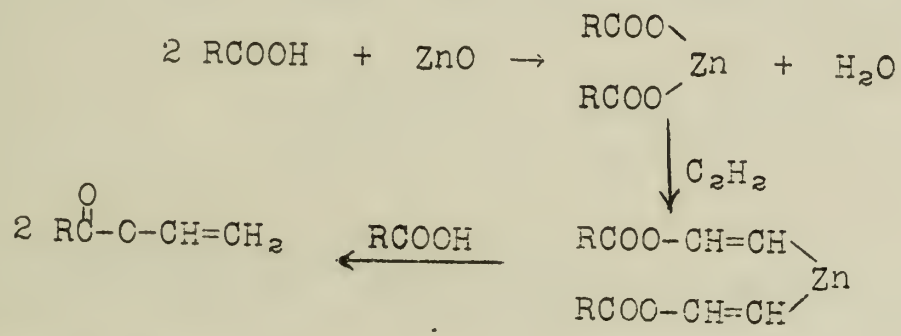
In a similar manner, 1,3-butanediol yields mostly the corresponding cyclic acetal.



1,4-Butylene glycol yields almost exclusively the 1,4-divinyl ether due to the greater distance between the hydroxy groups.
$HOCH_2-CH_2-CH_2-CH_2OH + HC\equiv CH \rightarrow CH_2=CH-O-CH_2CH_2CH_2CH_2-O-CH=CH_2$.

2. Polyhydroxystyrenes.--Acetylene reacts with phenols and aromatic hydroxy compounds in the presence of alkali catalysts to form vinyl ethers. However, when zinc or cadmium salts of organic acids are used as catalysts, the addition becomes nuclear, giving rise to the formation of polyhydroxystyrenes (5). Possibly the mechanism is a rearrangement of initially formed vinyl ethers. Poly-vinylisobutylphenol (Koresin) was made in this manner (6).

3. Vinyl esters of fatty acids.--Using zinc or cadmium salts of organic acids as catalysts, acetylene reacts with fatty acids under pressure to give vinyl esters. Esters of acids up to C_{18} have been prepared in this manner (7).

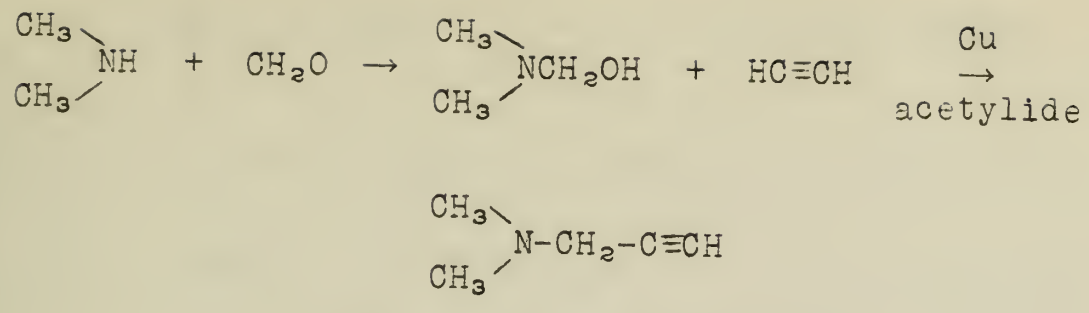


B. Ethynyl Compounds.

1. Propargyl amines.--Propargyl amines have been produced by several methods. Coffman (8) treated phenyl- or vinyl-acetylenes with alkanolamines by heating in dioxane solution to give the corresponding propargyl amines.

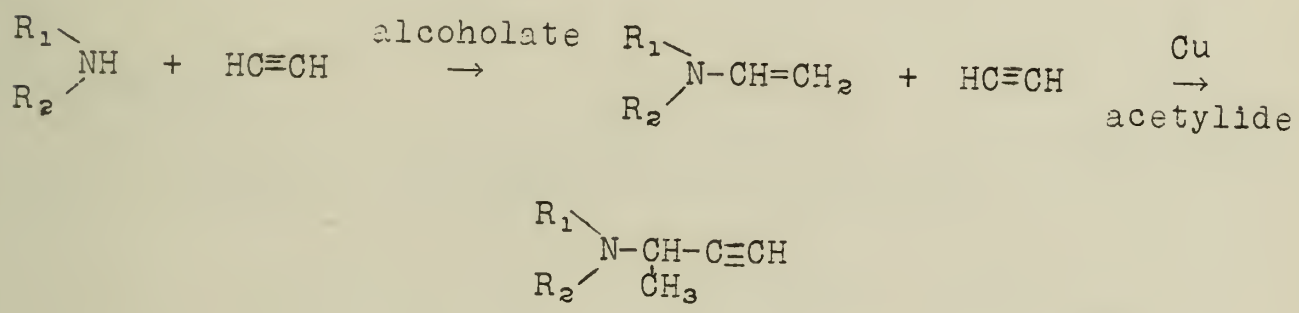
$$RC\equiv CH + HOR'NH_2 \rightarrow R-C\equiv C-R'NH_2$$

Direct addition of the acetylene is impossible unless the hydrogen atom of the acetylene is activated by a catalyst. Copper or silver acetylide serves this purpose. The synthesis of propargyl amines involves the use of this catalyst (9).

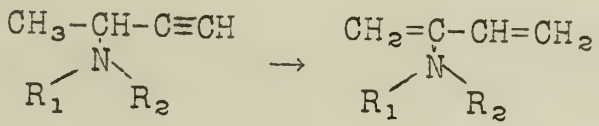


1-N-Dimethylaminopropyne-2

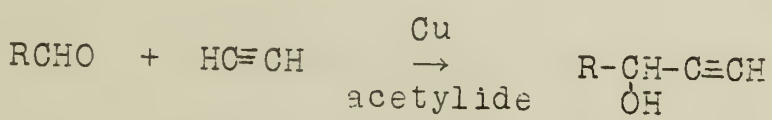
2. Aminobutynes.--As mentioned before, the use of alcoholates permits the formation of vinyl amines. The use of Cu or Ag acetylide permits the introduction of a second mole of acetylene (10).

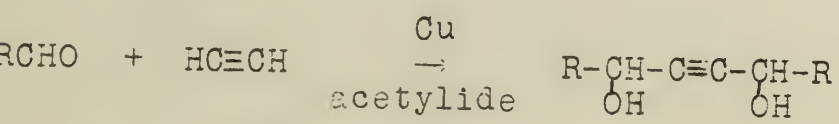


Aminobutynes can readily conjugate to give aminobutadienes.



3. Alkynols.--Aldehyde addition to acetylene can take place on either one side of the molecule, or on both sides.

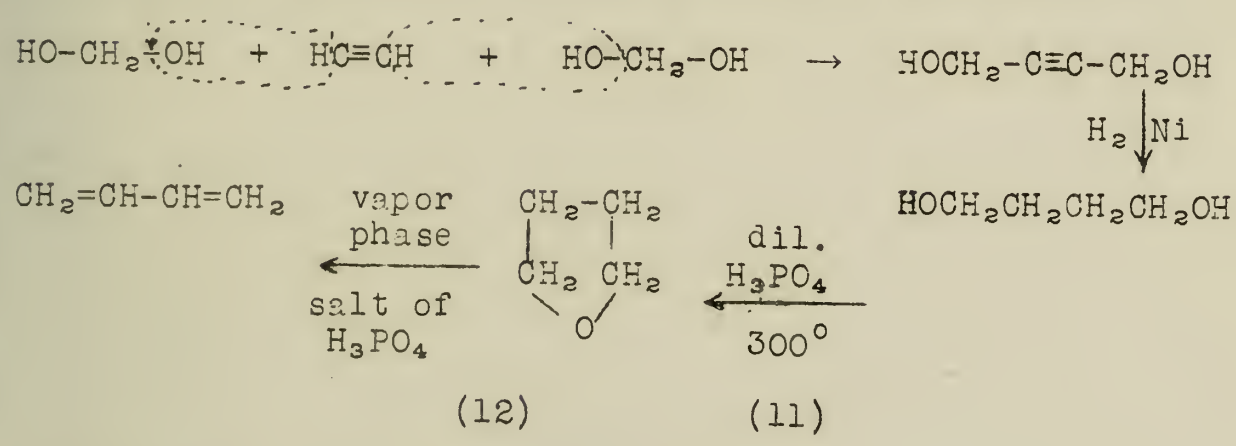




One of the most important uses of this reaction was the production of butadiene from acetylene and formaldehyde.

$$2\ HCHO + HC{\equiv}CH \xrightarrow[\text{acetylide}]{Cu} HOCH_2{-}C{\equiv}C{-}CH_2OH \qquad (6)$$

The aldehyde probably adds in the form of its hydrate,



C. Acrylates.

The use of the last catalyst, $Ni(CO)_4$, effects the addition of carbon monoxide to acetylene to give acrylates.

$$HC{\equiv}CH + CO + H_2O \xrightarrow{Ni(CO)_4} H_2C{=}CH{-}COOH$$

The use of alcohols in place of the water results in the formation of acrylic esters.

Addition of an alkali chloride to the catalyst permitted the direct addition of HCN to the acetylene to form acrylonitrile.

$$HC{\equiv}CH + HCN \xrightarrow[NaCl]{Ni(CO)_4} H_2C{=}CH{-}CN$$

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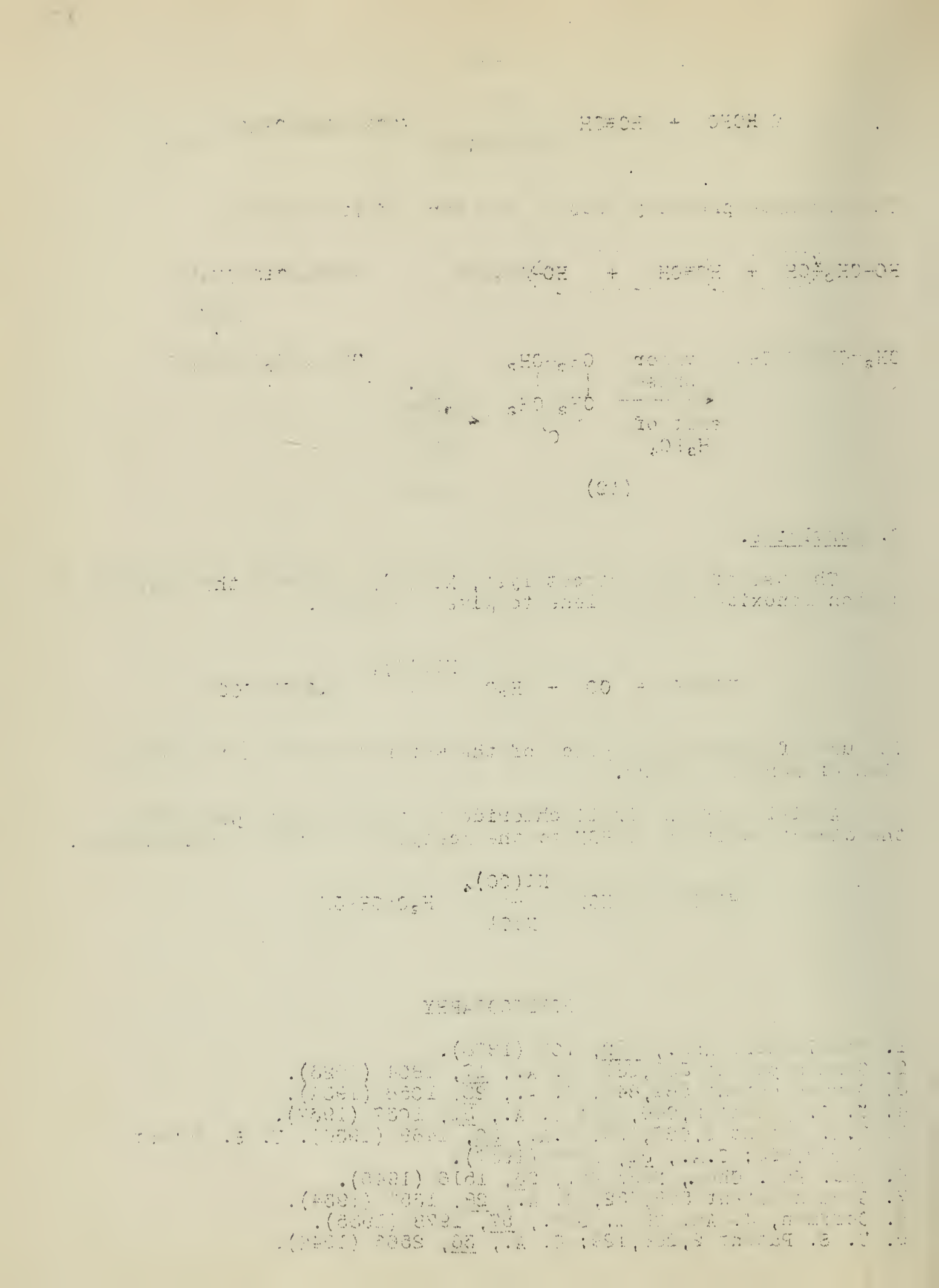

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(All patents except (2) issued to W. Reppe and associates, I. G. Farbenindustrie.)

Reported by R. L. Myers
November 14, 1945.

THE MECHANISM OF THE ALKYLATION REACTION

Louis Schmerling, Universal Oil Products Company

Isoalkanes are readily alkylated with olefins when treated thermally at high temperatures and pressure or when treated catalytically at room temperature with specific catalysts.

Composition fo the Products (Isobutane - Ethylene)

Thermal alkylation	Catalytic alkylation
2,3-Dimethylbutane	2,2-Dimethylbutane
2-Methylpentane	2-Methylpentane
Octanes	Octanes
Ethane	
Isopentane	

The products of thermal alkylation have been accounted for successfully by Frey and Hepp by assuming free radicals to be produced first which then take part in reaction chains.

A number of mechanisms have been proposed by different investigators for the catalytic alkylation. None of them is satisfactory either in explaining how the reaction occurs or accounting for the structure of the products obtained. After an extensive investigation of the reactions of alkyl chlorides with olefins and of isoparaffins with chloroolefins, Schmerling suggests a mechanism which appears to have none of the objectionable features of the previous ones and which seems to give a truer picture of what occurs during alkylation. The alkylation of isoparaffins with olefins in the presence of aluminum chloride, for example, proceeds via the conversion of the paraffin to an alkyl chloride. The mechanism is outlined below for the reaction of isobutane with ethylene. Similar reactions occur with other paraffins and olefins.

$$CH_3-\underset{CH_3}{\overset{H}{C}}-CH_3 + CH_2{:}CH_2 + HCl \rightarrow CH_3-\underset{CH_3}{\overset{Cl}{C}}-CH_3 + CH_3CH_3 \qquad (1)$$

$$CH_3-\underset{CH_3}{\overset{Cl}{C}}-CH_3 + CH_2{:}CH_2 \rightarrow CH_3-\underset{CH_3}{\overset{CH_3}{C}}-CH_2-CH_2-Cl \qquad (2)$$

$$CH_3-\underset{CH_3}{\overset{CH_3}{C}}-H + CH_3-\underset{CH_3}{\overset{CH_3}{C}}-CH_2-CH_2-Cl \rightarrow CH_3-\underset{CH_3}{CH} - \underset{CH_3}{CH}-CH_3 + CH_3-\underset{CH_3}{\overset{Cl}{C}}-CH_3 \qquad (3)$$

The t-butyl chloride formed in (3) starts a new cycle by reacting with ethylene as in (2). Evidence in support of each of the three steps has been found. All the other hydrocarbon products are ascribed by Schmerling to secondary reactions.

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Reported by T. L. Tan
November 21, 1945

ALLYLIC GRIGNARD REAGENTS

Forty years ago, Tiffeneau and Delange found that the action of formaldehyde on benzyl magnesium chloride produced o-tolyl carbinol. Since that time, allylic Grignard reagents and their structures have been studied extensively. There are usually two possible structures.

$$RCH = CHCH_2MgX \text{ (primary)} \quad \text{and} \quad R\underset{\underset{MgX}{|}}{C}HCH = CH_2 \text{ (secondary)}$$

The primary structure has been established when the allylic bond is actually part of the benzene ring. For the other cases, the structure has not been definitely determined. There are three factors contributing to the difficulty of assigning structures to the allylic Grignard reagents. (1) There may be allylic rearrangement during the formation of the reagent. (2) After the Grignard reagent is formed, there may be an equilibrium established between the primary and secondary forms. (3) There also may be rearrangement during the subsequent reactions of the reagent.

Products derived from the primary form of the Grignard reagent are classified as normal. Products with structures that would be expected from the secondary form are classified as abnormal.

Coleman and Forrester discovered that the reaction of monochloroamine on benzyl magnesium chloride gave benzyl amine, a normal product. Since monochloroamine produces abnormal products in some reactions it is probable in the case of benzyl magnesium chloride that the Grignard reagent has the normal structure and rearrangement takes place in subsequent reactions. The mechanism for such rearrangement involves the formation of a chelate ring in the complex formed from the Grignard reagent and the reactant.

Gilman and Harris, while studying the reactions of cinnamyl chloride, suggested that the rearrangement may take place during the formation of the Grignard reagent.

$$C_6H_5CH = CHCH_2Cl + Mg \rightarrow C_6H_5CH = CHCH_2- + MgCl-$$

$$C_6H_5CH = CHCH_2- \xrightarrow[\text{rearrangement}]{} C_6H_5\underset{\underset{|}{}}{C}HCH = CH_2$$

$$C_6H_5\underset{\underset{|}{}}{C}HCH = CH_2 \xrightarrow[MgCl]{} C_6H_5\underset{\underset{MgCl}{|}}{C}HCH = CH_2$$

Austin and Johnson assumed that the abnormal reagents entered the γ-position followed by migration of the hydrogen on the γ-carbon to the α-position.

$$H\underset{\underset{|}{}}{C} = \underset{\underset{|}{}}{C}CH_2MgCl \xrightarrow[RCOCl]{} RCO\underset{\underset{|}{}}{C}H-\underset{\underset{|}{}}{C} = CH_2 \rightarrow RCO\underset{\underset{|}{}}{C} = \underset{\underset{|}{}}{C}CH_3$$

Young has and is studying a number of reactions of allylic Grignard reagents with the idea of determining their sturcture and the exact mechanism of their reactions.

Different mixtures of crotyl and methyl vinyl carbinyl bromides were treated with magnesium. When the Grignard reagents were hydrolysed, there was formed a mixture of 1-butene, the abnormal product, and cis-2-butene and trans-2-butene, the normal products. The composition of the butene mixture was the same if butenyl chlorides were used instead of the bromides and was also the same no matter what mixture of butenyl bromides was used as starting material. This supported the hypothesis of a resonating intermediate ion formed at the instant that magnesium reacts with the butenyl bromide.

$$CH_3CH = CHCH_2: \longleftrightarrow CH_3\overset{\cdot\cdot}{C}HCH = CH_2$$

$$\begin{array}{ccc}
 & CH_3CH = CHCH_2Br & \\
 & \downarrow Mg & \\
 & H_2O \downarrow & \\
CH_3CH_2CH = CH_2 & CH_3-CH \parallel CH_3-CH & CH_3CH \parallel HCCH_3 \\
62\% & 30\% & 7\% \\
 & \uparrow Mg & \\
 & CH_3\underset{Br}{C}HCH = CH_2 &
\end{array}$$

Addition of dioxane to isomeric butenyl magnesium bromides forms a precipitate of a dioxane complex of RMgBr, leaving R_2Mg in solution.

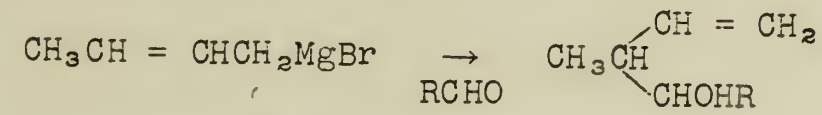
$$2RMgBr \rightleftarrows R_2Mg + MgBr_2$$

When the precipitate and the solution were hydrolysed, it is found that the average composition of the butenyl radicals from the precipitate and from the solution was the same regardless of the composition of the starting material.

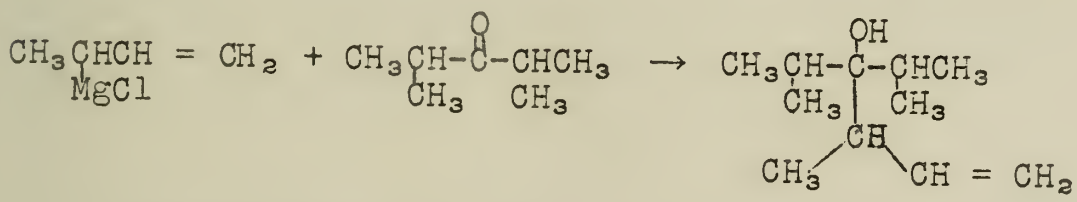
Carbonation of benzyl magnesium chloride resulted in a normal product; however, carbonation of cinnamyl magnesium chloride leads to an abnormal product. When a dilute ether solution of crotyl and methyl vinyl carbinyl bromides was treated with magnesium and poured on a large excess of solid carbon dioxide, there was a yield of 75% of 2-methyl-3-butenoic acid, the abnormal product.

$$\left.\begin{array}{c} CH_3CH = CHCH_2Br \\ \text{or} \\ CH_3\underset{Br}{C}HCH = CH_2 \end{array}\right\} \xrightarrow[Mg]{} \xrightarrow[CO_2]{} CH_3-\underset{COOH}{C}H-CH = CH_2$$

The addition of aldehydes and ketones to allylic Grignard reagents results in products of the secondary form of the Grignard reagent or abnormal products. It has been found that acetaldehyde, acetone, benzaldehyde, and propionaldehyde also form products derived from the secondary form.



The addition of butenyl Grignard reagent to diisopropyl ketone was investigated to test the generality of the formation of abnormal products when an allylic Grignard reacts with a carbonyl group. Both butenyl chloride and butenyl bromide gave high yields of the product derived from the secondary form of the ketone.



Coupling reactions of allylic Grignards take place readily. Young found that coupling butenyl magnesium bromide with the allylic bromide produced a mixture of products with the secondary form predominating. If the chloride was used instead of the bromide, even higher yields of 3-methyl-1,5-heptadiene, the secondary form, were obtained.

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Reported by Odette Shotwell
November 21, 1945.

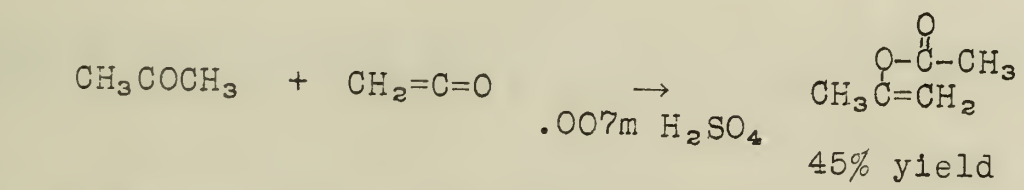
UNUSUAL REACTIONS OF KETENES

The structure of ketene can best be represented as a resonance hybrid between

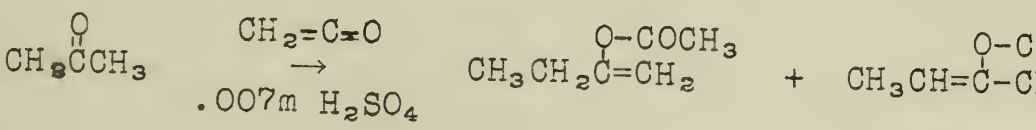
These structures parallel those for diazomethane.

The unusual reactivity exhibited by these compounds may be attributed to their highly unsaturated character.

Reactions of Ketenes with Carbonyl Compounds.--Degering and Gwynn found that ketones containing three alpha hydrogen atoms react with ketene to form the enol acetate. With acetone the reaction proceeds as follows.

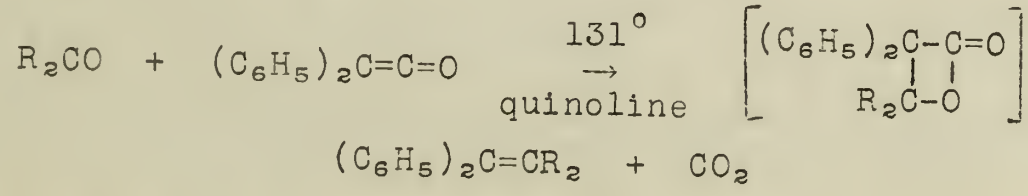


The reaction does not proceed when phosphoric acid of p-toluenesulfonic acid us used as a catalyst. When methyl ethyl ketone is used in the reaction, two isomeric products are obtained.



Mesityl oxide, acetophenone, and vinyl methyl ketone also form acetates with ketene. Diisopropyl ketone and pinacolone are only slightly reactive under similar conditions.

If ketones are treated with a higher ketene such as diphenyl ketene in the presence of quinoline, carbon dioxide is evolved and substituted olefins are formed.



This method is not generally useful, since under the conditions specified, extensive polymerization of the ketene occurs.

Aromatic aldehydes react with ketene when potassium acetate is present with the formation of mixed acid anhydrides.

$$\mathrm{ArCHO} \xrightarrow[\mathrm{KAc}]{\mathrm{CH_2{=}C{=}O}} \left[\mathrm{Ar{-}\underset{OH}{C}H{-}CH{=}C{=}O}\right] \xrightarrow{\mathrm{CH_2{=}C{=}O}} \left[\mathrm{Ar{-}\underset{OCOCH_3}{C}HCH{=}C{=}O}\right] \rightarrow$$

$$\mathrm{ArCH{=}CH{-}CO{-}OCOCH_3}$$

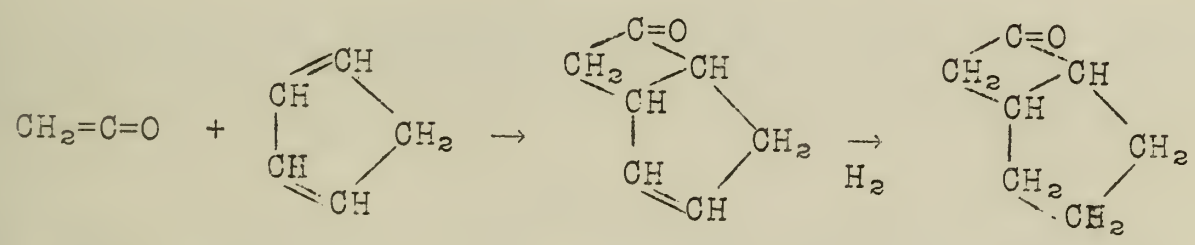
No reaction occurs when aliphatic aldehydes or ketones are substituted for the aromatic aldehyde. The use of higher ketenes such as diphenylketene blocks the course of the reaction.

Certain acid anhydrides enter into double decomposition reactions with ketenes, as is illustrated in the following equation.

$$2(\mathrm{C_6H_5CH_2})_2\mathrm{C{=}C{=}O} + (\mathrm{C_6H_5{-}\underset{C_6H_5}{C}{-}\overset{O}{C}{-}})_2\mathrm{O} \rightarrow 2(\mathrm{C_6H_5})_2\mathrm{C{=}C{=}O} +$$

$$(\mathrm{C_6H_5CH_2{-}\underset{CH_2C_6H_5}{C}{-}\overset{O}{C}{-}})_2\mathrm{O}$$

<u>Addition to Double Bonds</u>.--Brooks and Wilbert found that ketene would add to cyclopentadiene to form a ketone.



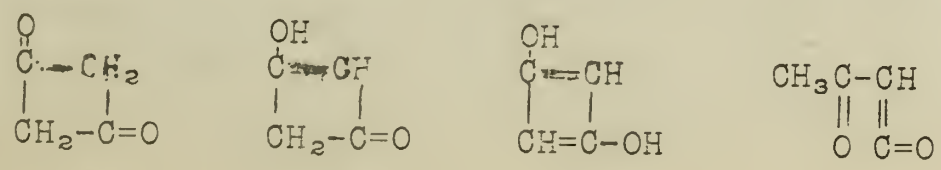
A semicarbazone was prepared from the unsaturated ketone and from its reduction product.

Diphenylketene reacts with the double bond of nitroso compounds

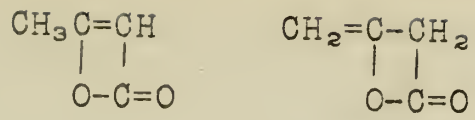
$$\begin{matrix}(\mathrm{C_6H_5})_2\mathrm{C{=}C{=}O} \\ + \\ \mathrm{O{=}NC_6H_5}\end{matrix} \rightarrow \begin{matrix}(\mathrm{C_6H_5})_2\mathrm{C{-}C{=}O} \\ \mathrm{O{-}NC_6H_5}\end{matrix} \underset{\Delta}{\rightleftarrows} (\mathrm{C_6H_5})_2\mathrm{C{=}O} + \mathrm{C_6H_5N{=}C{=}O}$$

Similar reactions occur when azobenzene or phenyl isocyanate is used in place of the nitroso compound.

<u>Formation of Ketene Dimer</u>.--When ketenes are allowed to stand, either in the presence or absence of catalysts, dimers form. The following formulas have been proposed for these dimers.



I II III IV



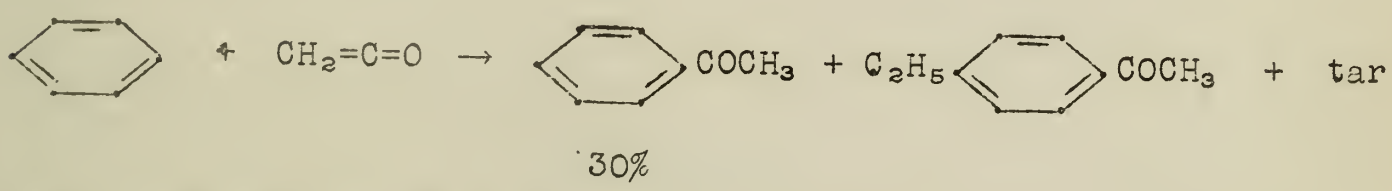
V VI

Examination by aseptic distillation revealed that the dimer is a single substance and is not a mixture of tautomeric forms. In addition it has been shown to have a planar configuration. Since gaseous ketene has a dipole moment of 3.53, the symmetrical formulas I and III must be outlawed. Ozonation produces pyruvic aldehyde. This would be the expected product only from formula IV. C. D. Hurd has proposed that the dimer can best be represented as a resonance hybrid between IV and V.

IV

This is supported by the observation that hydrogenation of ketene dimer yields the lactone of β-hydroxybutyric acid.

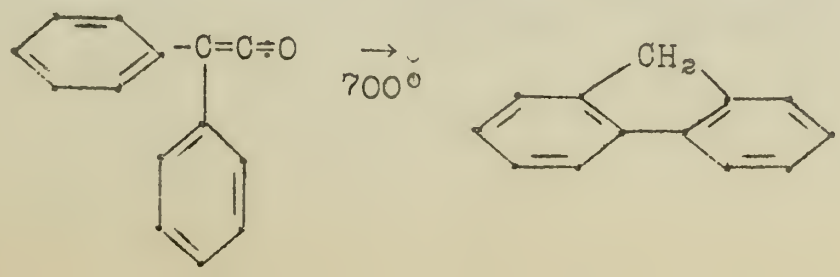
Friedel Craft Reactions with Ketene.--When ketene is used in place of acetic anhydride in the usual Friedel Craft procedure, the yield of the expected ketone is low; alkyl ketones are found to have been formed.



30%

When chlorobenzene is used, the only product capable of identification is 2-ethyl-3-chloroacetophenone. When ketene is pyrolyzed, ethylene is formed as well as methane, carbon, and carbon monoxide. An investigation of this reaction proved that the decomposition did not take place by a free radical mechanism. If the assumption is made that the Friedel Craft catalysts promote the pyrolytic decomposition at low temperatures, the observed products can be accounted for.

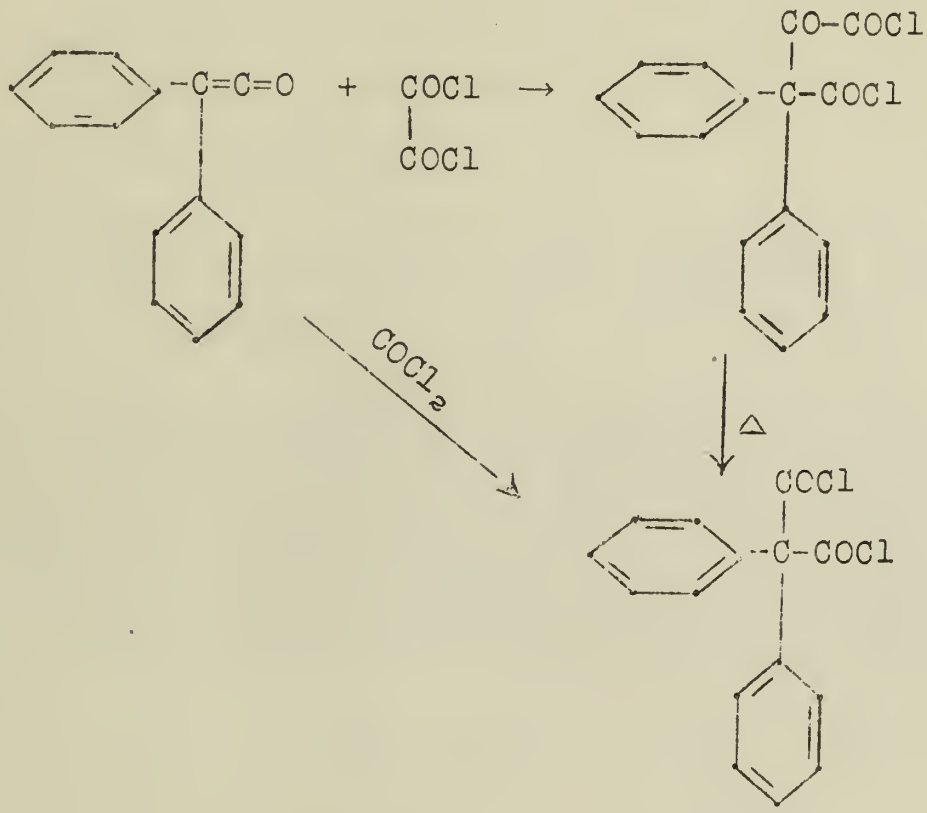
Other Reactions.--When diphenylketene is pyrolyzed, fluorene is formed.



Ketene will react with nitryl chloride to produce a mixture of chloro-acetyl chloride and nitro-acetyl chloride.

$$CH_2{=}C{=}O \;+\; NO_2Cl \;\rightarrow\; CH_2ClCOCl \;+\; NO_2CH_2COCl$$

Diphenylketene will react with phosgene or with oxalyl chloride as follows.



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Reported by H. D. Porter
November 28, 1945.

ORGANIC POLYVALENT IODINE COMPOUNDS

Organic polyvalent iodine compounds may be divided into four classes:

the iodoso salts	RIX_2
the iodoso compounds	RIO
the iodoxy compounds and	RIO_2
the iodonium compounds	R_2IX

where x can be Cl^-, $CH_3\overset{O}{C}-\bar{O}$, HSO_4^-, etc.

Iodoso compounds are readily obtained by treating iodoso salts with dilute aqueous solutions of alkali hydroxide or carbonate.

$$C_6H_5ICl_2 + 2NaOH \rightarrow C_6H_5IO + H_2O + 2NaCl$$

Mason and Hanby have carried out the direct substitution of aromatic hydrogen by the iodoso group by use of iodyl sulphate [$I_2O_3 \cdot SO_3$ or $(IO)_2SO_4$] prepared by dissolving iodine pentoxide in concentrated sulfuric acid. Nitrobenzene gave a 50-60 per cent yield of m-iodosonitrobenzene. This method could not be used with benzene or aromatic compounds containing ortho or para directing groups; the reaction of such compounds proceeded to produce iodonium compounds. The reaction can be represented by the following ionic exchanges:

$$IO^+ + 2H^+ \rightleftarrows I^{+++} + H_2O$$

$$I^{+++} + RH \rightarrow H^+ + RI^{++}$$

When ortho or para directing groups are present the reaction proceeds further to form the iodonium compound.

$$RI^{++} + RH \rightarrow H^+ + R_2I^+$$

Willgerodt showed that one of the best methods for the preparation of iodoso chlorides is to lead dry chlorine gas into an ice-cold solution of the aryl iodide dissolved in chloroform.

$$C_6H_5I + Cl_2 \rightarrow C_6H_5ICl_2$$

The iodoso chlorides of benzene, alkyl-, bromo-, chloro-, and nitro-substituted benzenes and naphthalenes have been prepared this way.

Iodoso chlorides have also been made by the action of hydrochloric acid on the corresponding iodoso or iodoxy compounds.

$$C_6H_5IO + 2HCl \rightarrow C_6H_5ICl_2 + H_2O$$

$$C_6H_5IO_2 + 4HCl \rightarrow C_6H_5ICl_2 + 2H_2O + Cl_2$$

Iodoxy compounds have been prepared by heating the corresponding iodoso compounds.

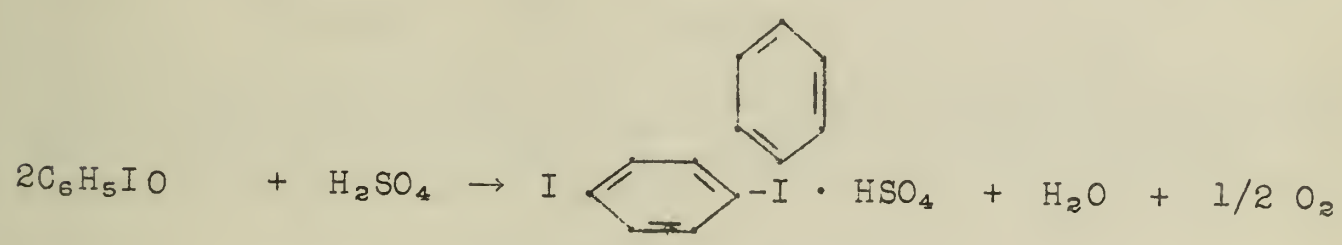
$$2C_6H_5IO \rightarrow C_6H_5I + C_6H_5IO_2$$

The heating is generally done in the presence of water so that steam distillation can be carried out. The organic iodide is volatile with steam; the iodoxy compound is not. Iodoxy compounds can also be prepared by the action of hypochlorous acid on iodoso compounds.

$$C_6H_5ICl_2 + 4HOCl \rightarrow C_6H_5IO_2 + 3Cl_2 + 2H_2O$$

$$C_6H_5IO + HOCl \rightarrow C_6H_5IO_2 + HCl$$

Iodonium compounds have been prepared by treatment of aromatic iodoso compounds with concentrated sulfuric acid. <u>Para</u> iodophenyl iodonium sulfate has been prepared this way.



Diphenyl iodonium hydroxide has been prepared by shaking equivalent quantities of iodosobenzene and iodoxybenzene with water and silver oxide.

$$C_6H_5IO + C_6H_5IO_2 + AgOH \rightarrow (C_6H_5)_2ICH + AgIO_3$$

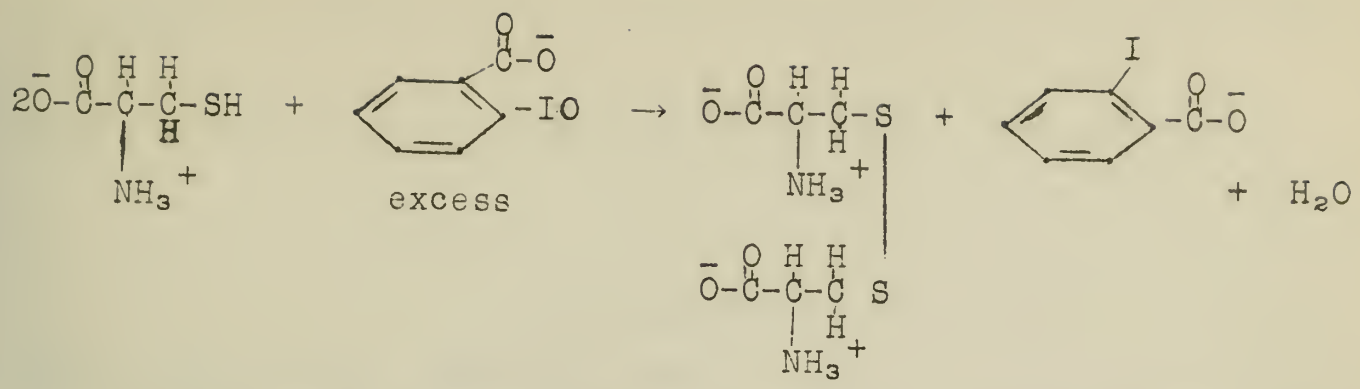
Aliphatic and mixed aliphatic aromatic iodonium compounds have been made by the action of iodoso dichlorides on the compound of silver chloride and silver acetylide.

$$2C_6H_5ICl_2 + HC{\equiv}CAg{\cdot}AgCl \rightarrow C_6H_5\underset{Cl}{I}{-}\underset{Cl}{C}{=}\underset{Cl}{C}{\cdot}H + C_6H_5I + 2AgCl$$

Iodoso compounds are quantitatively reduced to iodo compounds in aqueous acid by added iodide, and the free iodine can be titrated with standard thiosulfate solution.

$$C_6H_5IO + 2HI \rightarrow C_6H_5I + I_2 + H_2O$$

Aryliodoso compounds readily oxidize mercaptans. Standard <u>ortho</u> iodosobenzoate has been used in the quantitative determination of cysteine.



Phenyliodoso chloride has been used as a chlorinating agent, and it has been found that it gives the same products as chlorine but that it is much milder in its action. Unsaturated compounds such as benzalacetophenone and 2-pentene reacted, while cinnamic acid did not react.

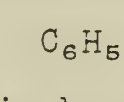
The iodoxy compounds are oxidizing agents comparable in strength to the iodates. They are much more stable than the iodoso compounds. They can also be quantitatively reduced in aqueous acid by potassium iodide.

$$C_6H_5IO_2 + 4HI \rightarrow C_6H_5I + 2I_2 + 2H_2O$$

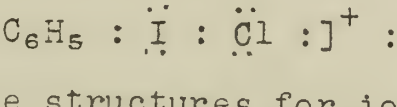
Iodonium hydroxides are strong bases comparable in strength to the quaternary ammonium bases. Both the hydroxides and the salts decompose on heating. For example, diphenyl iodonium iodide decomposes to give iodo benzene.

$$(C_6H_5)_2I \cdot I \rightarrow 2C_6H_5I$$

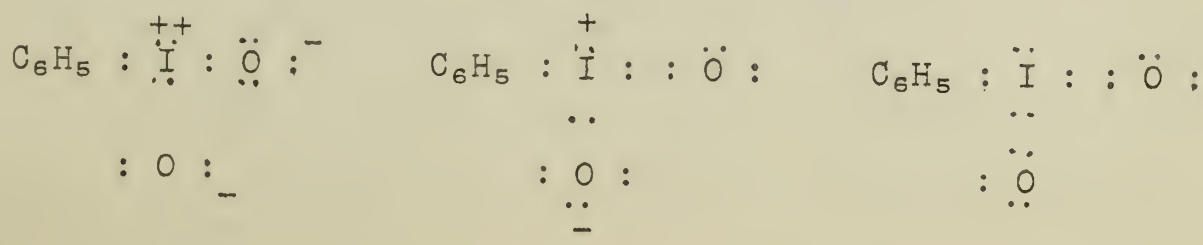
The structures of organic polyvalent iodine compounds are best shown by electronic formulas. For example, iodosobenzene is given a structure which contains two-covalent iodine.



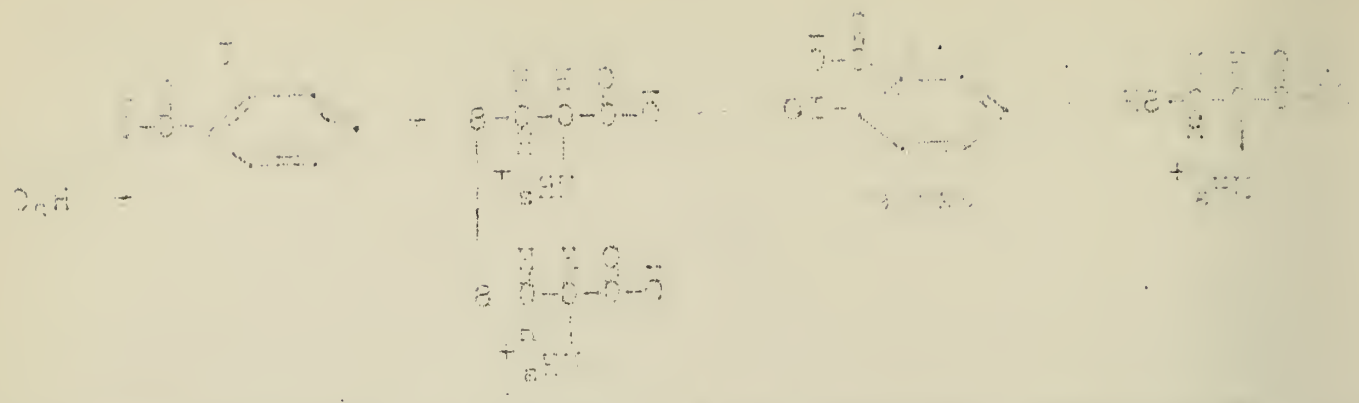
Phenyl iodoso chloride is best represented by the following structure:



There are three possible structures for iodoxybenzene. Structures I and II have been favored by various investigators.



I II III



The iodonium compounds can be represented by the following ionic structure:

$$[R : \overset{R}{\underset{\cdot\cdot}{I}} :]^{+} X^{-}$$

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Reported by S. L. Meisel
November 28, 1945.

SOME ASPECTS OF THE REACTIONS OF FREE RADICALS IN SOLUTION

Free radicals in solution can be highly selective in their action. Not only do the reactions which free radicals undergo vary greatly in the energy of activation necessary, but the free radicals themselves vary in reactivity.

The Alkyl Free Radicals.--The free methyl radical is one of the most reactive and may be generated in a number of ways.

1. $CH_3COO\text{-}OOC\text{-}CH_3 \xrightarrow[\Delta]{} CH_3\cdot + CH_3COO\cdot + CO_2$

2. $PhMgBr + CH_3Br \xrightarrow{CoCl_2} \text{Biphenyl} + CH_3\cdot$

The following mechanism has been postulated.

a) $PhMgBr + CoCl_2 \rightarrow PhCoCl + MgBrCl$
b) $2PhCoCl \rightarrow \text{Biphenyl} + 2(\cdot CoCl)$
c) $CH_3Br + CoCl\cdot \rightarrow CH_3\cdot + CoClBr$

The following mechanism explains the different products obtained when bromobenzene is used,

a) $CH_3MgBr + CoCl_2 \rightarrow CH_3CoCl + MgBrCl$
b) $CH_3CoCl \rightarrow CH_3\cdot + \cdot CoCl$
c) $PhBr + \cdot CoCl \rightarrow Ph\cdot + CoClBr$

and should be noted here. Benzene and methane are the chief products and only a small amount (3 percent) of biphenyl is obtained. The free methyl, formed in ether ease in 80 to 90% yield, reacts immediately with the solvent in which it is prepared.

$$CH_3\cdot + C_2H_5OC_2H_5 \xrightarrow{65\%} CH_3\underset{\bullet}{C}H\text{-}O\text{-}C_2H_5 + CH_4$$
$$CH_3\cdot + C_2H_5OC_2H_5 \xrightarrow{35\%} CH_3OC_2H_5 + C_2H_5\cdot$$

$$CH_3\cdot + CCl_4 \rightarrow CH_3Cl + \cdot CCl_3$$

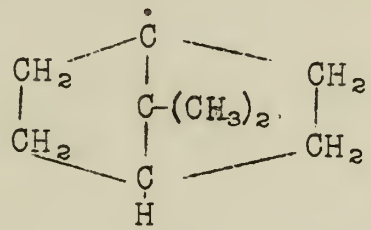
The other lower (up to butyl) aliphatic free radicals may be prepared in an analagous manner. The decomposition of acetyl, n-butyryl and iso-butyryl peroxides by heating in carbon tetrachloride solution gave 10 to 20% yields of methyl, isopropyl, and n-propyl chlorides. When the normal aliphatic free radicals are generated by the cobaltous chloride method, the following products are obtained.

Halide (+PhMgBr + $CoCl_2$)	Products
CH_3Br	CH_4 62% of gas analyzed C_2H_6 18% C_2H_4 20%
CH_3CH_2Br	C_2H_6 40% C_2H_4 60%
$CH_3CH_2CH_2Br$	C_3H_8 54% C_3H_6 46%
$CH_3CH_2CH_2CH_2Br$	C_4H_{10} 54% C_4H_8 46%

Tertiary Alkyl Free Radicals.--When trimethylacetyl peroxide is heated in carbon tetrachloride solution, no t-butylchloride is formed. When the t-butyl radical is generated by the cobaltous chloride method it disproportionates. The products consist of 80% i-butane and 20% i-butylene.

The decomposition of the highly stable di-1-apocamphane carboxylic peroxide in carbon tetrachloride gave the following products.

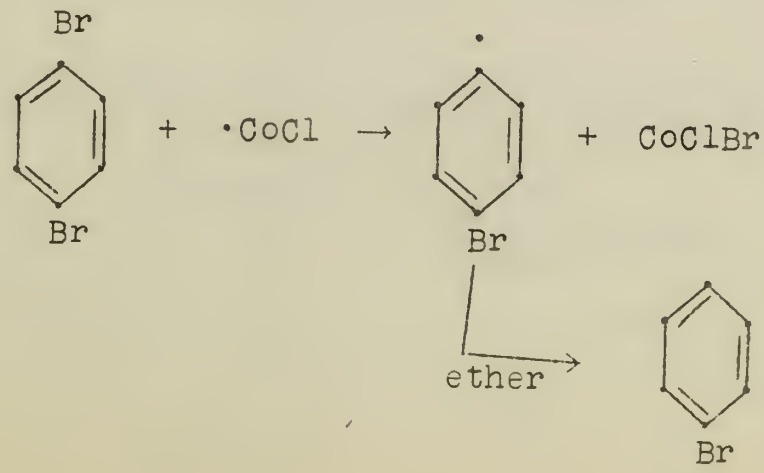
R• =



RCl	RR	RCOOR	RCOOH	C_2Cl_6
36%	9%	50%	5%	

Aromatic Free Radicals.--The free phenyl radical has the same order of reactivity as the free methyl radical. The aromatic radicals have been thoroughly discussed elsewhere.

A new reaction, however, is the following.



The reduction is non-selective and has been shown to proceed with o-m-, and p-dichloro and dibromobenzene to give about 50% of the monohalo compound; and with p-bromobiphenyl, 1- and 2-bromonapthalene, 9-bromoanthracene, 9-bromophenanthrene, 2-bromofluorene, and 3-bromo acenapthene to give 44 to 57% yields of the reduced product.

Dimerization of Free Radicals.--Any free radical which is not reactive enough to abstract a hydrogen atom might conceivably dimerize. The following radicals have been shown to do so.

		Dimer	Unsat. Compd.	Sat. Compd.	CH_4
cyclohexyl chloride	($+CH_3MgBr+CoCl_2$)	26%	29%	27%	85%
(cis) 2-methylcyclohexyl chloride	($+CH_3MgBr+CoCl_2$)	22%	31%	34%	83%
(trans) 2-methylcyclohexyl chloride	($+CH_3MgBr+CoCl_2$)	27%	23%	28%	77%
bornyl chloride	($+CH_3MgBr+CoCl_2$)	63%	20%	15%	72%
isobronyl chloride	($+CH_3MgBr+CoCl_2$)	31%	44%	19%	77%
benzyl bromide		couples			
anethole hydrobromide	($+PhMgBr+CoCl_2$)	42%			
2-phenyl-2-bromopropane		couples			
1-phenyl-3-chloropropane	($+BuMgBr+CoCl_2$)	<15%	24.5%	46%	82%
cinnamyl chloride	($+CH_3MgBr+COCl_2$)	70%			

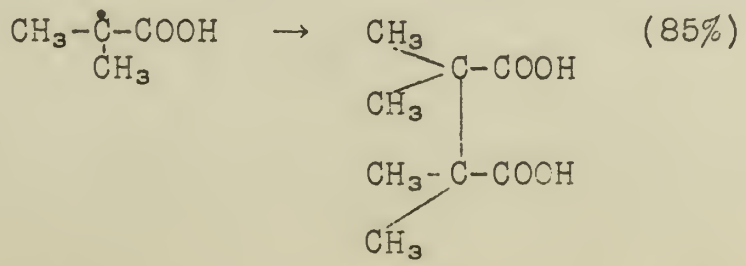
A more general and useful method of producing free radicals which dimerize, may be illustrated by the following.

$$\underset{(.144\ \text{mole})}{CH_3COO\text{-}OOCCH_3} \xrightarrow{\Delta} CH_3\cdot \quad CH_3COO\cdot \quad + \quad CO_2$$

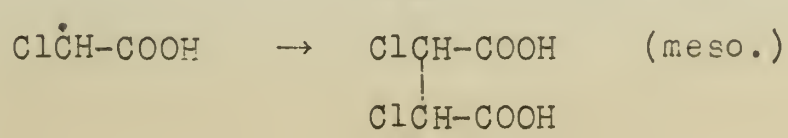
$$\underset{(\text{solvent})}{CH_3COOH} \quad + \quad CH_3\cdot \quad \rightarrow \quad \cdot CH_2COOH \quad + \quad CH_4$$

$$2\ \cdot CH_2COOH \rightarrow \begin{array}{l} CH_2\text{-}COOH \\ | \\ CH_2\text{-}COOH \end{array} \qquad (.072\ \text{mole})$$

Acetyl, propionyl or benzoyl peroxides may be used. The following radicals have been shown to dimerize by this method.



(85%)



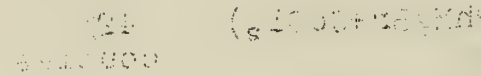
(meso.)

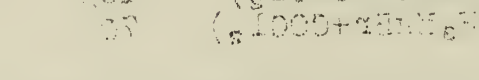
The reduction is non-selective and has been shown to [illegible] with 2-Br-, and p-chloro and dichloro-, to give above [illegible] of the month's compound; [illegible] with p-bromo-phenyl, 1- and 2-bromonaphthalene, 2-bromo-[illegible] ether, 2-bromofluorene, and [illegible] to give [illegible] of the reduced product.

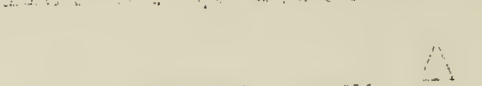
Dissociation of Free Radicals. Many free radical [illegible] reactive enough to abstract a hydrogen atom, might conceivably dimerize. The following radicals have been shown to do so:

	Dimer	Sat.
	Diam. Conp.	Compd.
cyclohexyl chloride (+CH_3,[illegible]+CCl_4)	36%	22%
(cis) 2-methylcyclohexyl chloride (+CH_3,[illegible]+CCl_4)	22%	31%
(trans) 2-methylcyclohexyl chloride (+[illegible]+CCl_4)	22%	44%
bornyl chloride (+C_6H_5,[illegible]+CCl_4)	27%	28%
isobornyl chloride (+CH_3,[illegible]+CCl_4)	69%	20%	28%
benzyl bromide (+CH_3,[illegible]+CCl_4)	21%	44%	18%
an ungle hydrobromide	complex		16%
2-phenyl-2-bromopropane (+C_6H_5,[illegible]+CCl_4)	42%		
1-phenyl-2-chloropropane	complex		
cinnamyl chloride (+C_6H_5,[illegible]+CCl_4)	76		
(+C_6H_5,[illegible]+CCl_4)	+ 18%	22.5%	40%

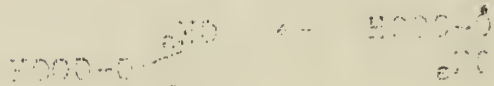
A more general and useful method of producing free radicals which dimerize, will be illustrated by the following.

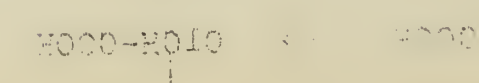






Acetyl, propionyl or benzoyl peroxides do [illegible]. The following radicals have been shown to dimerize by this method.





Kharasch has postulated that relative electronegativity determines whether a radical dimerizes or disproportionates.

The Addition of Free Radicals to Double Bonds.--Most of these reactions are well known. They include the peroxide catalyzed addition of HBr, H_2S, RSH, HSO_3^-, and SO_2Cl_2. Kharasch, Jensen and Urry have recently developed the following new free radical additions.

1. $RCH{=}CH_2 + CCl_4 \rightarrow RCHClCH_2CCl_3$
   $RCH{=}CH_2 + CHCl_3 \rightarrow R{-}CH_2{-}CH_2{-}CCl_3$

Some examples of the compounds thus prepared are:

CCl_4 + n-octene-1 $\rightarrow C_6H_{13}CHClCH_2CCl_3$
2 CCl_4 + diallyl $\rightarrow Cl_3CCH_2CHClCH_2CH_2CHClCH_2{-}CCl_3$
CCl_4 + diallyl $\rightarrow CH_2{=}CH{-}CH_2{-}CH_2{-}CH_2{-}CH_2{-}CCl_3$

The yields are better than 60%.

2. $RCH{=}CH_2 + CHCl_2COOCH_3 \rightarrow RCH_2CH_2{-}CCl_2COOCH_3$ 40%

$RCH{=}CH_2 + CCl_3COCl \rightarrow R{-}CHCl{-}CH_2{-}CCl_2COCl$ 81%

$RCH{=}CH_2 + CH_2ClCOOCH_3 \rightarrow RCH_2{-}CH_2CHCl{-}COOCH_3$ 10%

(yields are for R = C_6H_{13}).

The by-products for octene-1 and methyl dichloroacetate are probably

$Cl_2C{-}COOCH_3$
|
$Cl_2C{-}COOCH_3$

and

$RCH_2{-}CH_2{-}RHR{-}CH_2{-}CCl_2{-}COOCH_3$

3. $RCH{=}CH_2 + PCl_3 \rightarrow RCHClCH_2PCl_2$

$RCH{=}CH_2 + RPCl_2$ is being investigated.

(R = C_6H_{13})

All three reactions are run at or below 100°; in the presence of an excess of the olefin and about 2 to 10 mole percent of diacetyl peroxide. The postulated intermediate radical is formed from the halide to be added, for example; $\cdot Cl_2C{-}COOCH_3$. R in every case must be aliphatic or else either polymerization will occur or the chain reaction will not propagate.

Marvel, Dec, and Corner have found that triphenyl methyl and tribiphenyl methyl add to styrene, vinylacetate, p-chlorostyrene and m-nitrostyrene to give products composed of one molecule of olefin and two molecules of free radical.

Formation of Stable Free Radicals-Inhibition.--Polymerization to double bonds requires relatively little energy. Furthermore, the radicals involved in the chain reaction are reactive, although quite selective in their action. Those substances which act as inhibitors or retarders are compounds which will react with a chain-propagating radical to form a radical of greater stability. Examples of such substances are, nitrobenzene, nitroethylene, thymol, m-cresol, benzoquinone and ethyl- and diethylbenzene.

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Reported by F. E. Woodward
December 5, 1945.

[illegible]

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[illegible] benzene.

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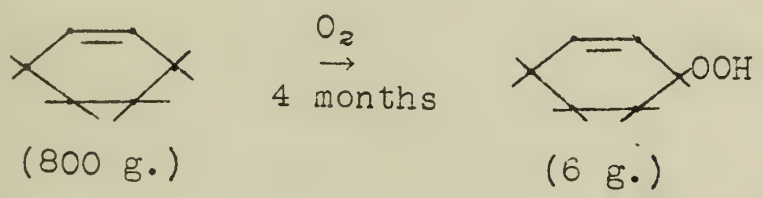
Approved by F. E. Woodward
December 1, 1948.

AUTOXIDATION OF HYDROCARBONS

Autoxidation may be defined (1) as spontaneous oxidation by free oxygen. As applied to hydrocarbons, the reaction accomplishes introduction of a functional group into an inert molecule and has aroused interest as a possible cheap source of alcohols and ketones. From the standpoint of yields, these investigations have been disappointing, but alcohols and ketones are obtained in high yields from decomposition of the intermediate peroxides.

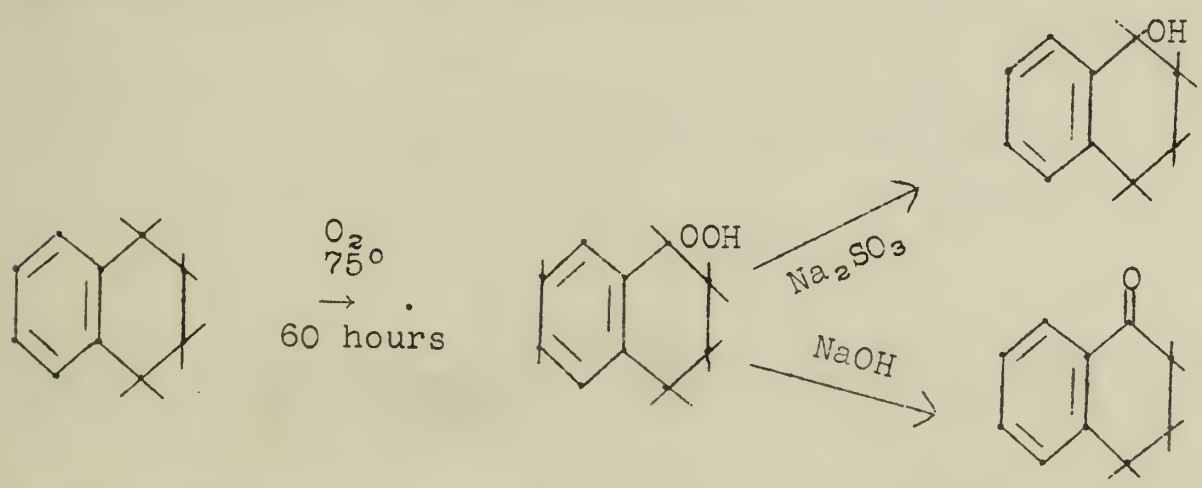
In 1903, Weger (2) noticed that pure samples of cumene, hydrindene and tetralin formed strongly acidic materials when exposed to air in the presence of light. The acidic nature of these products was attributed to peroxides.

The peroxides, which may be considered as intermediates in all autoxydations, had not been isolated and characterized until Stephens (3) succeeded in purifying cyclohexene hydroperoxide by distillation.



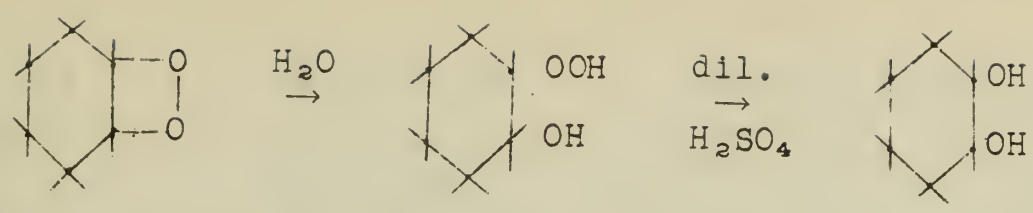
(B.P. 54-6°/0.5mm.)
(Mol. Wt. 117)

Later, Hock (4) isolated the hydroperoxide of tetralin and, depending upon the conditions employed for decomposition, obtained either α-tetralone or α-tetralol.



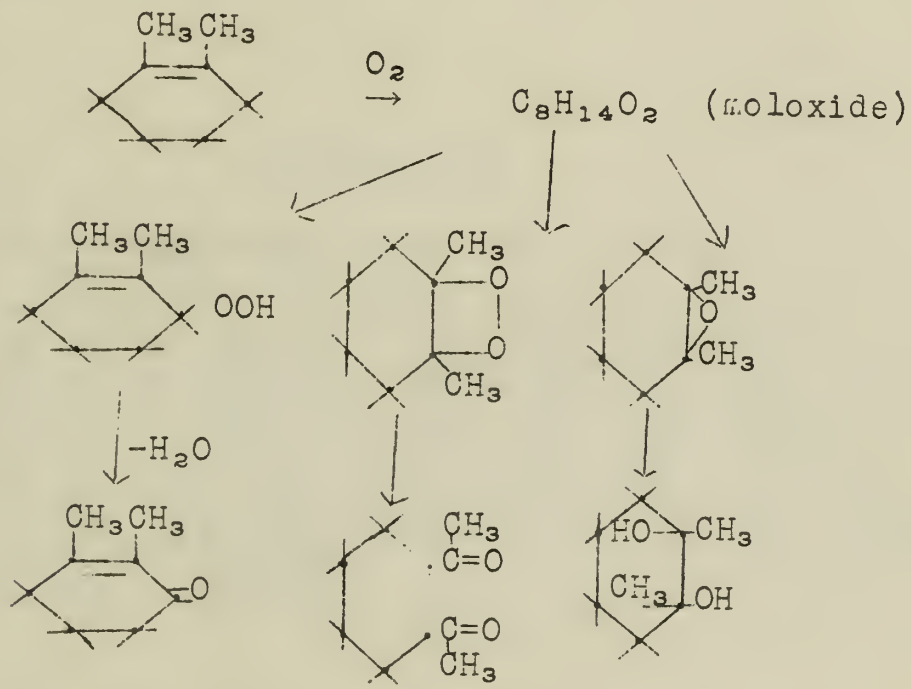
As autoxidation of tetralin proceeded in fair yield, and within a relatively short time, Hock and his coworkers (4-12) undertook a thorough study of the reaction as applied to readily available hydrocarbons.

When cyclohexene was used, although these workers obtained the same peroxide as Stephens, they assigned it a cyclic structure, since 1,2-cyclohexanediol could be obtained in 50% yields by acidic decomposition.



Decomposition of the peroxide with base yielded 60-65% of cyclohexenol and a complicated mixture from which were characterized formic, acetic, glutaric, adipic, α-hydroxyadipic and oxalic acids. These acids were separated by fractionation of their methyl esters.

The problem of assigning a structure to a peroxide also arose for Dupont (13) when autoxidation of 1,2-dimethylcyclohexene produced a mixture of three compounds which he believed came from three different oxides.



Application of the reaction to open-chain olefins, such as 1-hexene, afforded very low yields of peroxide, even after a reaction time of 200 hours.

$$CH_3CH_2CH_2CH_2CH{=}CH_2 \xrightarrow[\text{200 hrs.}]{O_2} CH_3CH_2CH_2\underset{\underset{OOH}{|}}{C}H{=}CH_2 \xrightarrow{Na_2SO_3}$$

$$CH_3CH_2CH_2\underset{\underset{OH}{|}}{C}H{=}CH_2$$

Other olefins were found to give equally poor yields.

Returning to the substituted aromatic hydrocarbons, Hock and Lang investigated several compounds in search of those which might form peroxides in good yield.

Hydrocarbon	Yield of Peroxide
hydrindene	5 %
*p-menthene	15
p-xylene	0.4
ethylbenzene	0.7
octahydroanthracene	15
cumene	6-7
diphenylmethane	5

*Prepared (in 90% yield) by dehydration of menthol with $ZnCl_2$.

The compounds listed represent the most promising of those investigated and the emphasis has shifted from a search for hydrocarbons which respond to autoxidation to a search for possible catalysts for the reaction.

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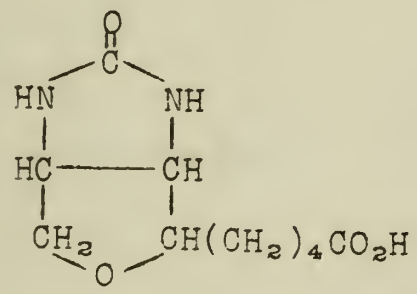
Reported by R. E. Jones
December 5, 1945.

SYNTHESIS OF dl-OXYBIOTIN

Klaus Hofmann, University of Pittsburgh

A series of papers on the reactions of substituted furans and tetrahydrofurans has been published by Hofmann. These led to the synthesis of an analog of biotin which has been named dl-oxybiotin. This is a compound in which the sulfur atom of biotin has been replaced by an oxygen atom.



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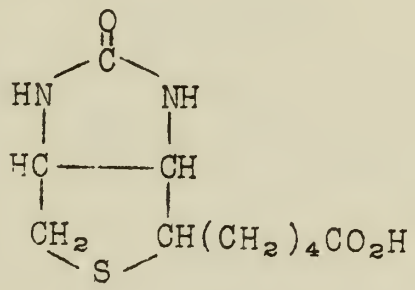
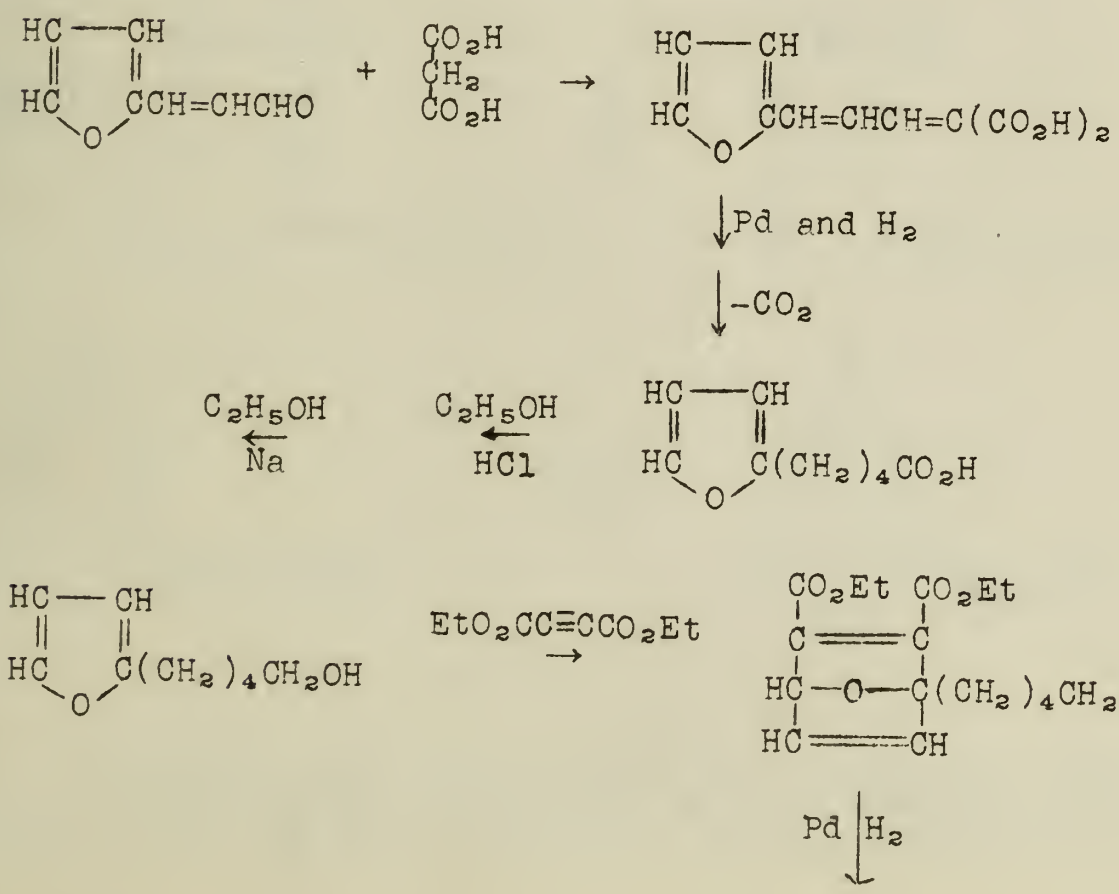
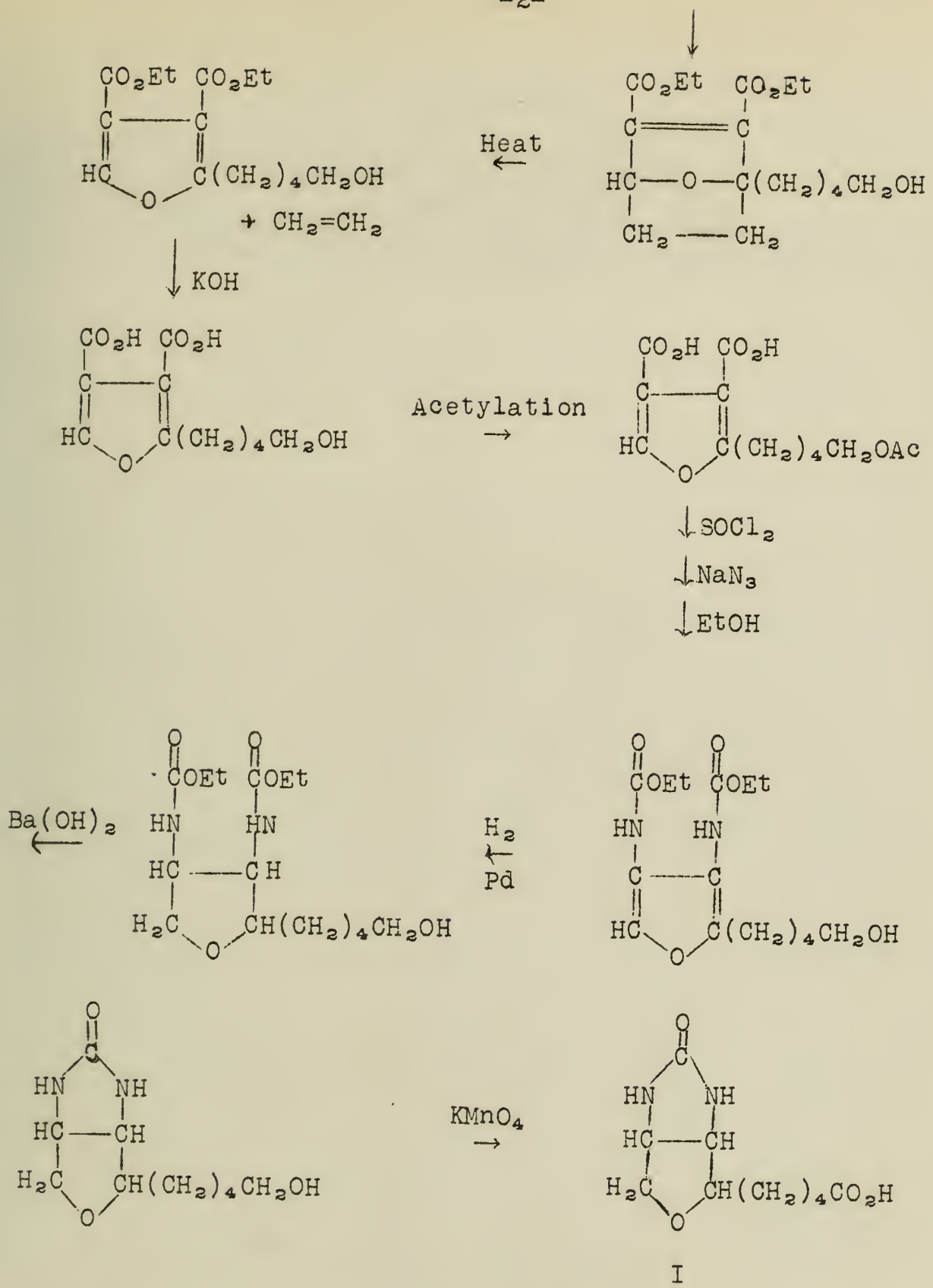
Oxybiotin



Biotin

The synthesis followed this scheme.





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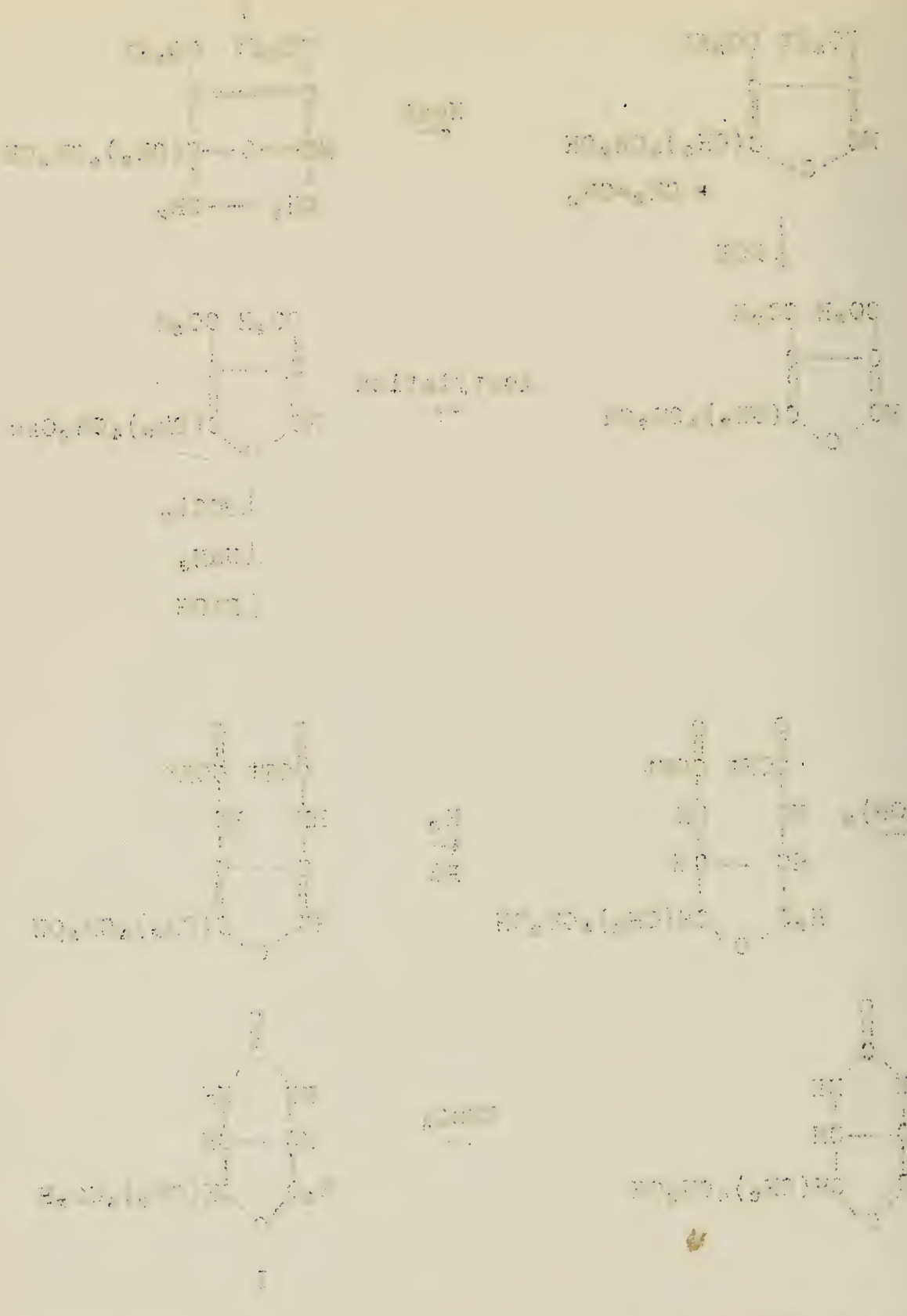
The product I was not resolved but the dl form showed high yeast growth activity. From this fact the author believes that oxybiotin has a spacial arrangement corresponding to that of biotin.



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Reported by N. R. Easton
December 12, 1945.

RECENT DEVELOPMENTS IN THE IDENTIFICATION OF ORGANIC COMPOUNDS

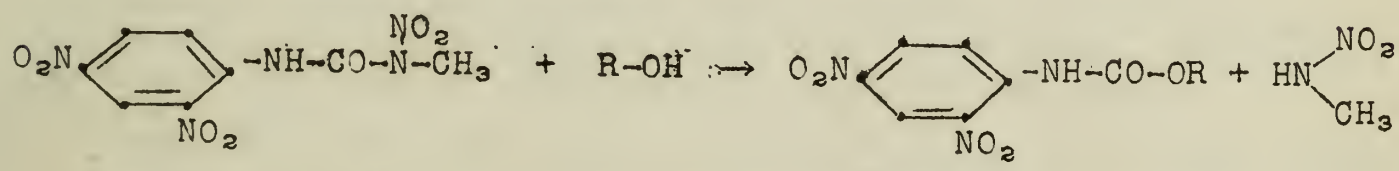
The last discussion of this topic was given by Quentin F. Soper on April 22, 1942. An attempt has been made to include in this seminar most of the pertinent articles which have appeared since that time. Methods which do not appear to be of rather general applicability have been omitted.

I. Alcohols.--Green and Green have applied the method of Seikel and Huntress to the preparation of the trityl (triphenylmethyl) ether of propylene glycol. The derivative is easily prepared and has a sharp and characteristic melting point.

Armstrong and Copenhaver have prepared the p-nitrobenzoyl esters of alcohols through eicosyl. In most cases, these are satisfactory derivatives.

Meadoe and Reid propose pseudo-saccharin chloride as a convenient reagent for the identification of primary and secondary alcohols and phenols. They list the melting points of the derivatives of thirty-one alcohols and seven phenols.

Van Glinkel reports that the 2,4-dinitrophenyl urethans are useful derivatives for the identification of alcohols. These compounds cannot be prepared directly from 2,4-dinitrophenyl isocyanate since this compound is unknown. They are, instead, formed indirectly by the reaction between an alcohol and 1-(2,4-dinitrophenyl)-3-methyl-3-nitrourea.



The reagent is prepared readily from acetyl chloride, sodium azide, aniline and nitric acid. It may be used for the preparation of good derivatives of many primary, secondary and tertiary alcohols, and also of many glycols. It is not suitable for the identification of methanol, since the substituted methyl urethan is formed by heating the reagent alone in benzene under the type conditions used for preparing the derivatives. It does not appear to be very suitable for the identification of phenols. The properties of the derivatives of thirty-three hydroxyl compounds are tabulated. Their melting points are somewhat higher than those of some other types, and the author emphasizes their ease of crystallization.

S-Benzylthiuronium chloride has been used by Bair and Suter to identify alcohols. The alcohol is treated first with chlorosulfonic acid, and the alkyl hydrogen sulfate thus formed is

allowed to react with the reagent. In most cases, the salts obtained have fairly high, fairly sharp melting points. The melting points of the derivatives of fifteen alcohols (primary and secondary) and one glycol are listed.

Shupe recommends the potassium alkyl xanthates for the identification of alcohols, since these compounds have definite melting points in many instances, and also have easily determinable iodine equivalents which are directly related to their molecular weights. These derivatives are regarded as especially useful for the characterization of certain glycols and glycol mono ethers. The melting points and iodine equivalents of derivatives of eight alcohols, three glycols, six glycol mono ethers and one amino alcohol are listed.

Dewey and Witt have developed a procedure for the identification of alcohols by means of the optical properties of their carbanilates (phenylurethans). This technique is particularly useful when dealing with mixtures of alcohols or with aqueous alcohols, in which cases the melting points of the solids obtained from the unknown and phenylisocyanate would be useless. The crystallographic and optical properties of thirty-eight normal, primary alcohol carbanilates are given.

II. Acids.--Gilman and Abbott have used the thallous salts to characterize sulfonic acids. They are easily prepared in high yield and crystallize readily to give generally high-melting solids. One method of preparation allows the determination of the neutral equivalent. The melting points of fourteen thallous sulfonates are given.

Dermer and Dermer identify certain organic acids by determining their partition between ethyl ether and water. Constants for sixty-one acids of widely differing types are given.

Spatt and Schneider report a similar method on a micro scale.

Allen has used 1,2-dialkylsulfonylethanes to identify aliphatic sulfinic acids. The normal alkyl sulfinic acids from methyl through hexadecyl have been characterized in this way.

Pokras and Bernstein have shown that the presence of alkali chloride in the reaction mixture may interfere with the identification of acids by reaction with p-bromophenacyl bromide. Confusion may be caused by precipitation of p-bromophenacyl chloride instead of the expected ester.

III. Aldehydes and Ketones.--Von Wacek and Kratzl have employed the benzylthiuronium salts of the bisulfite compounds of aldehydes and ketones as characteristic derivatives. This type would be especially useful when an unknown carbonyl compound was isolated and purified as the bisulfite compound. The

properties of nine of these derivatives are tabulated.

Dugan and Haendler propose 4-aminomorpholine as a reagent for the identification of aromatic aldehydes. 4-(p-aminophenyl) morpholine may also be used. Data are given for the derivatives of nine aromatic carbonyl compounds.

Veibel, Blaaberg and Stevns have prepared the p-carboxyphenylhydrazones of 48 aldehydes and ketones. In general the melting points are not sharp since decomposition usually occurs. However, the neutral equivalents of the derivatives and hence the molecular weights of the carbonyl compounds can be determined by titration against standard alkali.

IV. Alkyl Benzenes.--Ipatieff and Schmerling have extended their previous work on the characterization of the monoalkylbenzenes to include isobutylbenzene. The mono- and diacetamino and the monobenzamino derivatives of this hydrocarbon are reported.

V. Alkyl and Aryl Hydrogen Sulfates.--Bair and Suter's work on the alkyl compounds has been discussed above under alcohols.

Barton and Young have devised a procedure for the identification of monoaryl sulfates which involves the preparation of the p-toluidine salts. These derivatives are nicely crystalline and they melt sharply. The melting points of six monoaryl sulfate--p-toluidine salts are listed.

VI. Amides.--Phillips and Pitt have developed a simple procedure for the identification of carboxylic acid amides which involves condensation with xanthydrol. The derivatives form rapidly, and are easily purified, crystalline solids with high melting points. The derivatives of twenty two monoamides and two imides are described.

Phillips and Frank have extended the use of this reagent to the characterization of aryl sulfonamides, for which purpose it is equally satisfactory. The properties of twelve aryl sulfonamide derivatives are given.

Williams, Rainey and Leopold have prepared the mercury derivatives of fifteen aliphatic and aromatic carboxylic acid amides. These products are high-melting crystalline solids which are satisfactory for purposes of identification.

Both the xanthydrol and the mercury schemes are applicable only to primary amides.

VII. Amines.--Plein and Dewey have shown that amines may be identified by means of the optical properties of their diliturate (5-nitrobarbiturate) salts. The method may be

applied to pure amines or to mixtures. The optical properties of the dilituratee of a large number of amines of varied types are tabulated.

Birch has developed 2-isonitrosocyclohexane-1,1'-pyridinium chloride as a reagent for the identification of primary and secondary aliphatic amines. The derivatives of ten amines are given.

VIII. Amino Acids.--Allen and Van Allen have extended previous work on the identification of aromatic amine sulfonic acids by listing the melting points of eleven more substituted chlorobenzenesulfonamides. These derivatives are prepared by replacement of the amino group by chlorine, followed by amidation.

IX. Amino Alcohols.--Jones recommends the hydrochlorides as suitable derivatives for a number of these compounds.

Shupe finds that the benzenesulfonyl, p-toluenesylfonyl and p-bromobenzenesulfonyl derivatives of amino alcohols are satisfactory for identification purposes. The reaction occurs at the amino group. The oxalates may also be used.

X. Aryl Iodides.--Many of these compounds may be identified by means of their iodosochlorides, as shown by Nichol and Sandin. Iodine equivalents of the derivatives may be determined.

XI. Barbiturates.--Castle and Poe find that many barbiturates may be identified by means of their condensation products with various substituted benzyl halides. p-Nitrobenzyl bromide is the reagent of choice. Derivatives of twenty-four barbiturates are described.

XII. Nitriles.--Rovira and Palfray have developed a new method for the hydrolysis of nitriles to acids. The nitriles are heated with potassium hydroxide in diethylene glycol or glycerol. The acids serve as derivatives.

Cutter and Tarr recommend the reduction of aliphatic nitriles to amines, followed by reaction with phenyl isothiocyanate to form substituted phenylthioureas.

XIII. Sugars.--Wolfrom and Karabinos recommend the identification of aldose sugars by conversion to their mercaptal acetates. The properties of sixteen such derivatives are given.

Hearon, Hiatt and Fordyce have prepared mono, di- and tricarbanilates of α- and β-methyl-d-glucosides. They are valuable derivatives of these glucosides.

The method of identification of sugars by the microscopic appearance of their crystalline osazones has been known for

some time. Hassid and McCready present photomicrographs of an extended list of these compounds. Derivatives of hexosephosphates, of especial interest in biochemistry, are included.

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Reported by J. B. Ziegler, Jr.
December 12, 1945

α-ALKOXYSTYRENES

α-Alkoxystyrenes may be regarded as the product of alkylation of the enol form of acetophenone, although they are not actually prepared in this manner. α-Ethoxystyrene was reported by Claisen in 1898 (1), who obtained it by the distillation of acetophenone diethyl acetal at atmospheric pressure.

$$C_6H_5\overset{(OC_2H_5)_2}{C} - CH_3 \xrightarrow{\Delta} C_6H_5\overset{OC_2H_5}{C} = CH_2 + C_2H_5OH$$

This method lead to a mixture of the enol ether and the acetal which apparently could not be separated by fractional distillation. The acetals can be quantitatively converted to the unsaturated compound by refluxing them with an acid chloride or phosphoric anhydride in the presence of a tertiary amine such as pyridine. A catalytic method in which the acetal is slowly passed through a column containing finely divided nickel heated to 180° has also been developed (2). Moureau (3) prepared his acetals indirectly by the addition of alcohol to an acetylenic acid followed by decarboxylation of this product.

$$RC\ CCO_2R' + 2R''OH \xrightarrow{NaOR''} \overset{(OR'')_2}{RC}-CH_2CO_2R' \rightarrow \overset{(OR'')_2}{RC}-CH_3$$

Other methods of preparing the ethers include the addition of an alcohol to styrene in the presence of iodine (4),

$$C_6H_5CH=CH_2 + ROH \xrightarrow{H_2O,\ I_2} C_6H_5\overset{OR}{C}H-CH_2I \xrightarrow{KOH} C_6H_5\overset{OR}{C}=CH_2$$

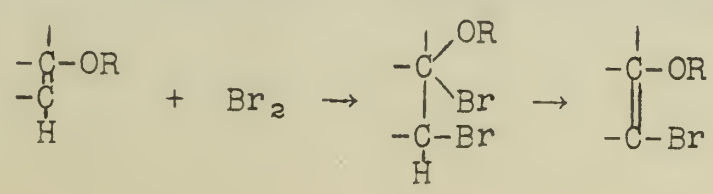
and dehydrohalogenation of β-halogen ethers obtained by the Boord method (5).

$$\underset{H}{\overset{Br\ OR'}{RCH-CBr}} + R''MgX \rightarrow \underset{H}{\overset{Br\ OR'}{RCH-C}}-R'' \xrightarrow{KOH} RCH=\overset{OR'}{C}R''$$

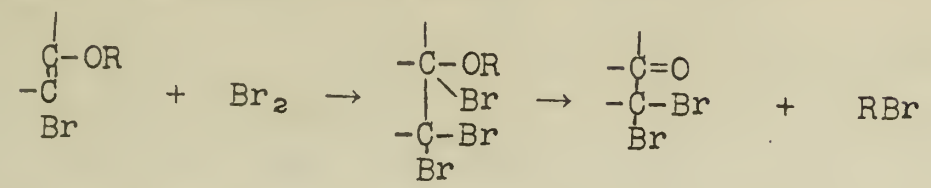
α-Alkoxystyrenes react like ketals in that they are readily hydrolyzed to ketones in the presence of a trace of acid.

$$C_6H_5\overset{OR}{C}=CH_2 \xrightarrow{H_2O,\ H^+} C_6H_5\overset{O}{C}CH_3 + ROH$$

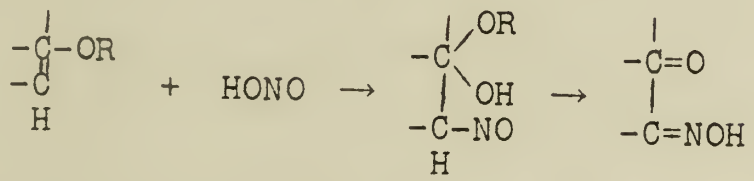
The double bond does not undergo addition reactions in the normal manner. Thus with bromine, a mole of hydrogen bromide is evolved for each mole of bromine which reacts. Meyer (6) pictures the reaction as follows.



If the reaction conditions are made more vigorous by heating, a second mole of bromine will react.

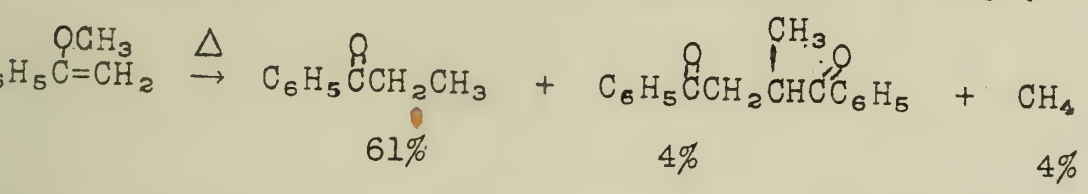


Similar results are obtained when nitrous acid is used as the addend.

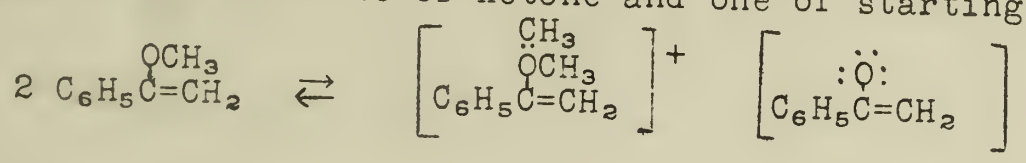


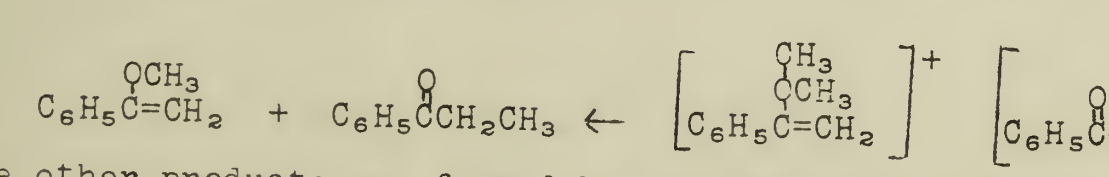
The enol ethers react with diazonium hydroxides to form a stable compound. Analysis shows that a molecule of alcohol is lost in the process, but no structure has been assigned to the product.

α-Alkoxystyrenes undergo a molecular rearrangement when heated to temperatures in the neighborhood of 250°.

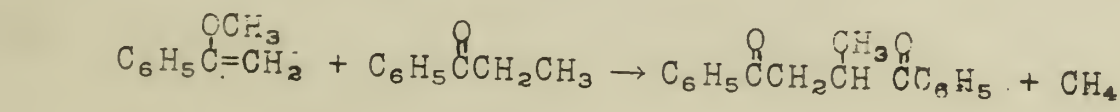


This reaction has been carefully studied (7 and 8) and a logical mechanism has been proposed. The first step has been shown to be a bimolecular reaction in which two molecules of the enol ether form a complex. This then breaks down to give the original reactants or one molecule of ketone and one of starting material.





The other products are formed by the reaction of a molecule of the ketone with one of the styrene.



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Reported by E. R. Trumbull
December 19, 1945

THE CHLORINATION OF FLUORO COMPOUNDS

(Albert L. Henne, Ohio State University)

Organic chloro-fluoro-compounds were first prepared by Swarts by the action of antimony trifluoride on polychloro compounds. In 1930 this reaction was extended by Midgley and Henne to the industrial preparation of the Freons. The unusual stability of these compounds instigated a more detailed study of the preparation and properties of such compounds. The following table lists a number which have been prepared by direct chlorination of various fluoro compounds.

Chlorination of Fluoro Compounds

Compound	Conditions	Products
CHF_3	Quartz, bright sunlight	$CClF_3$
CH_3CHF_2	Gaseous chlorine, sunlight	CH_3CF_2Cl, CH_2ClCF_2Cl 70% 6%
CH_3CF_3	Sunlight	CCl_3CF_3 (no intermediates detected)
$CH_3CF_2CH_3$	Sunlight	Stepwise to $CH_3CF_2CCl_3$, then to $CCl_3CF_2CCl_3$
$CH_3CFClCH_2Cl$	Sunlight	Stepwise to $CH_3CFClCCl_3$, then to $CCl_3CFClCCl_3$
$CH_3CH_2CF_3$	Sunlight, water present	Stepwise to $CCl_3CH_2CF_3$, one step to $CCl_3CCl_2CF_3$
$CH_3CH_2CF_2CH_3$	Sunlight	$CH_3CF_2CHClCH_3$ and $CH_3CF_2CH_2CH_2Cl$ (random distribution)
$CH_3CF_2CHClCH_3$	Sunlight	$CH_3CF_2CCl_2CH_3$ and $CH_3CF_2CHClCH_2Cl$ 2 parts 3 parts
$CH_3CF_2CH_2CH_2Cl$	Sunlight	$CH_3CF_2CH_2CHCl_2$, then $CH_3CF_2CH_2CCl_3$ and $CH_3CF_2CHClCHCl_2$ 7 parts 1 part
$CH_3CH_2CH_2CF_3$	Sunlight	$CH_3CHClCH_2CF_3$ and $CH_2ClCH_2CH_2CF_3$ 4 parts 5 parts
$CH_3CHClCH_2CF_3$	Sunlight	$CH_3CCl_2CH_2CF_3$ and $CH_2ClCHClCH_2CF_3$ 8 parts 6 parts
$CF_3CH_2CH_2CH_2Cl$	Sunlight	$CF_3CH_2CH_2CHCl_2$ and $CF_3CH_2CHClCH_2Cl$ 2 parts 1 part
$CF_3CH_2CH_2CHCl_2$	Sunlight	$CF_3CH_2CH_2CCl_3$
$CH_3CF_2CF_2CH_3$		$CH_3CF_2CF_2CCl_3$ (small amounts of intermediates)
$CH_3CF_2CF_2CCl_3$	Sunlight	One step to $CCl_3CF_2CF_2CCl_3$
$CF_3CH_2CF_2CH_3$	Sunlight	$CF_3CH_2CF_2CCl_3$ (intermediates present)
	Quartz, ultra violet light	$CF_3CCl_2CF_2CCl_3$
$CF_3CH_2CF_3$	all attempts at chlorination failed	

These results indicate the influence of two or more fluorine atoms on the same carbon atom in directing chlorination away from the adjacent carbon, so long as that carbon atom is not chlorinated. This influence extends, although weakly, to the γ-carbon atom. A further tendency in such reactions is to replace all hydrogen atoms linked to a given carbon atom once substitution is started, before hydrogen atoms attached to other carbon atoms are effected.

To explain this effect Henne states that a combination of the electronegativity of the fluorinated group with the condensed nuclei of such a group results in increased acidity of the hydrogen atoms on the adjacent carbon atom. This increased acidity protects against chlorination. To investigate this hypothesis the following synthesis was attempted which took advantage of the supposed acidity of the hydrogen atoms. Since every step in the synthesis was practically quantitative as assumed, the hypothesis seems well founded.

$$CF_3CH_2CH_2CH_3 \xrightarrow[\text{glass sunlight}]{Cl_2} CF_3CH_2CCl_2CCl_3 \xrightarrow{\text{mild alkali}}$$

$$CF_3CH{=}CClCCl_3 \xrightarrow{SbF_3} CF_3CH{=}CClCF_3 \xrightarrow{Cl_2}$$

$$CF_3CHClCCl_2CF_3 \xrightarrow{\text{mild alkali}} CF_3CCl{=}CClCF_3 \xrightarrow{Cl_2}$$

$$CF_3CCl_2CCl_2CF_3$$

Direct action of chlorine in the presence of iron has led to chlorination of aromatic fluoro compounds, giving compounds that would be expected due to an ortho-para directing influence. This work, largely carried out by Verma, is summarized below.

Compound chlorinated	Product
Fluorobenzene	p-chlorofluorobenzene 74%
p-Chlorofluorobenzene	an inseparable mixture assumed to be 2:4- and 3:4- dichlorofluorobenzenes
o-Fluorotoluene	2-fluoro-6-chlorotoluene 18% 2-fluoro-5-chlorotoluene 59%
p-Fluoronitrobenzene	2-chloro-4-nitrofluorobenzene
m-Fluorotoluene (no carrier)	m-fluorobenzal chloride

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Organic Reactions, Vol. II.

Reported by Wyvona Alexander
December 19, 1945.

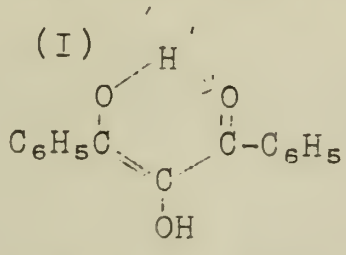
BENZOYLFORMOIN

A. H. Blatt

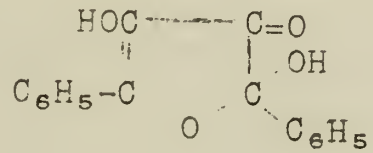
Benzoylformoin is formed by treating the product obtained from isonitrosoacetophenone and acetyl chloride with sodium carbonate solution.

From considerations which follow, Blatt concluded that benzoylformoin is a tautomeric mixture of the ene-diol(I) and the dihydroxyfuranone(II).

(I)



(II)



$C_6H_5COC(OH)=C(OH)COC_6H_5$
(III)

$C_6H_5COCHOHCOCOC_6H_5$
(IV)

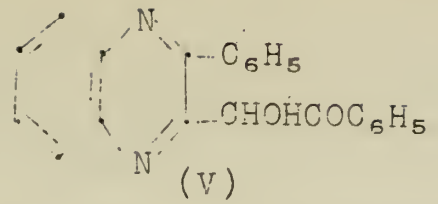
Although the structure (III) of the alternative ene-diol and the structure (IV) of the hydroxy ketone may be considered as possibilities, the entire behavior of benzoylformoin may be accounted for on the basis of an equilibrium between (I) and (II).

The formulation of benzoylformoin as an ene-diol is supported by salt formation, oxidation and quinoxaline formation.

A copper derivative of the formoin was obtained whose composition corresponds to the replacement of two atoms of hydrogen by one of copper. However, it was not ascertained as to which of the two possible ene-diols was involved.

Benzoylformoin is oxidized to diphenyl tetraketone by nitric acid, bromine and thionyl chloride. Karrer has shown by iodine titrations that the formoin exists in 46% aqueous alcohol as the ene-diol to the extent of 60%. Upon distillation, the stable yellow form yields a deep red liquid distillate which gradually changes to the more stable yellow modification. Since the color of the distillate resembles that of the unstable compound formed by acidification of an alkaline solution of the formoin, it has been proposed that the liquid is the ene-diol (given the chelate structure because of its greater volatility) and that the stable crystalline form is the dihydroxyfuranone. Treatment of benzoylformoin with copper acetate in aqueous acetic acid yields benzil. The oxidative elimination of carbonyl groups from linear tri- and tetraketones is a general reaction, also having been observed in the case of dibenzoyl carbinol and 2,4,6,-trimethylbenzoylformoin.

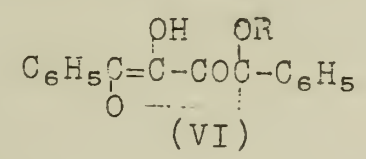
The quinoxaline (V) is formed by the reaction of benzoylformoin with o-phenylenediamine.



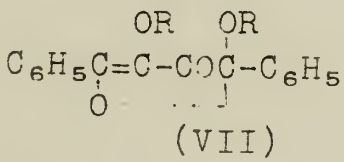
(V)

This product may be considered as formed from the ene-diol (I) since enolization of the hydroxy ketone system occurs readily even in the quinoxaline.

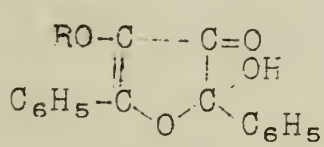
Benzoylformoin when dissolved in an alcohol and treated with hydrogen chloride forms a monoalkyl derivative (VI) and, further, a dialkyl derivative (VII) can be formed from the monoalkylation product by treatment with an alcoholate and alkyl iodide. The dialkyl derivative (VII) on solution in sulfuric acid loses one alkyl group to form a monoalkyl benzoylformoin (VIII) isomeric with the monoalkylation product obtained from benzoylformoin itself. By using dialkyl derivatives containing two different alkyl groups Abenius showed that the alkyl group introduced by means of alcohol and acid was always the one eliminated by treatment with sulfuric acid. On the basis of extensive investigation, Blatt assigned the following structures to the above compounds:



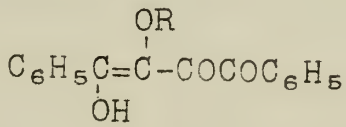
(VI)



(VII)



(VIII)

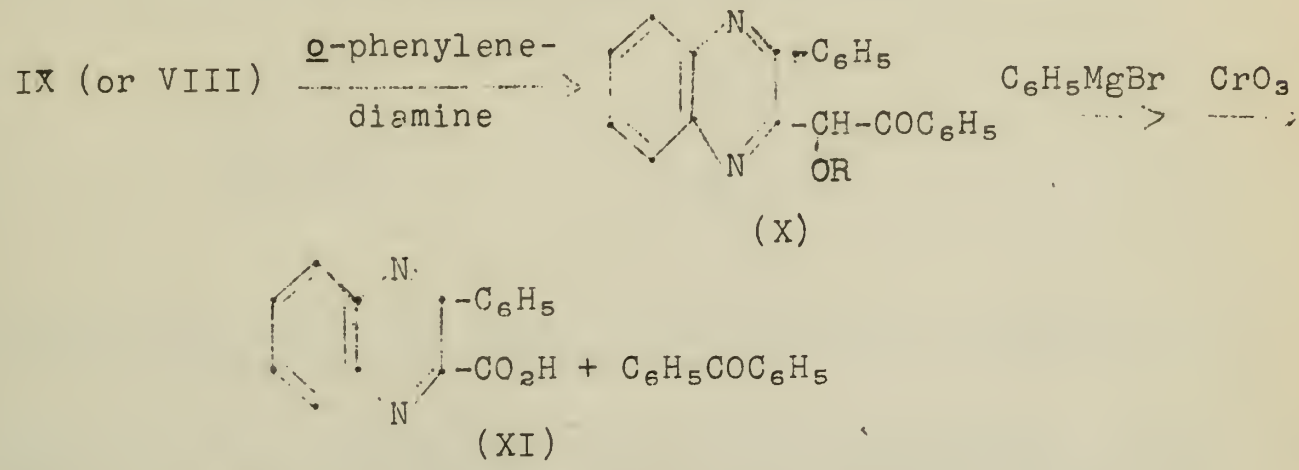


(IX)

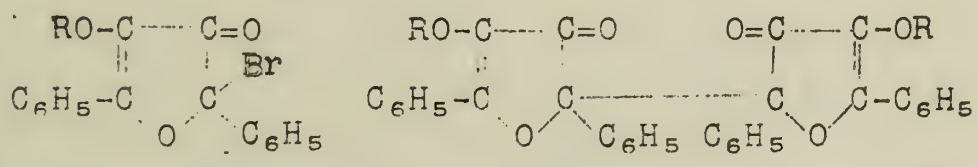
The formation of the monoalkyl derivative (VI) suggests a glycosidic structure and its behavior is consistent with this structure. Although no definite products could be isolated after acid hydrolysis, definite evidence for the reversibility of the glycoside formation was obtained by establishing the occurrence of alkyl interchange in an acid medium. Of the three alkylated products, only the cyclic monoalkyl derivative (VI) is oxidized to diphenyl tetraketone by the same acid oxidizing agents which convert benzoylformoin to the tetraketone. In addition, it does not react with o-phenylenediamine nor with hydroxylamine hydrochloride.

The evidence for the structure of the monomethyl derivative (VIII) was also of prime importance in indicating the structures of the other two products. Like benzoylformoin, it shows the behavior of a tautomeric mixture of the two forms: (VIII) and

(IX). On distillation it furnishes a red modification, presumably (IX), whose color is analogous to that of the alkaline solutions of the ether. It forms with o-phenylenediamine the quinoxaline (X) which on addition of phenylmagnesium bromide and subsequent oxidation is converted into benzophenone and 3-phenylquinoxaline-2-carboxylic acid (XI).



Compound (VIII) can be converted to the dialkyl derivative (VII) by means of methyl alcohol and hydrogen chloride, a type of etherification characteristic of tertiary alcohols and glycosides. This observation along with the unreactivity of the dialkyl compound toward o-phenylenediamine and toward phenylhydrazine suggests the structure (VII). That this compound is a glycosidic ether is shown by the removal of one alkyl group, the glycosidic group, by acid hydrolysis. Also, alkyl interchange involving the glycosidic group can be effected in acid medium. Treatment of the dialkylfuranone (VII) with hydrogen bromide yields the bromofuranone (XII) and also a bimolecular reduction product (XIII).



(XII) (XIII)

However, certain observations are in less accordance with the proposed structures. An unusual reaction involving the dialkyl benzoylformoin is the alkaline hydrolysis of the glycosidic alkyl group to produce the monoalkyl ether (VIII). Furthermore, the formoin and its open chain monoalkyl derivatives do not undergo a benzilic acid rearrangement with alkali alone.

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Holland, Organic Chemistry Seminar, University of Illinois, Jan.8,193

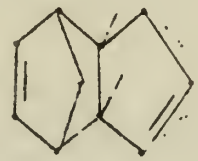
Reported by Peter Kovacic
January 9, 1946

THE CHEMISTRY OF DICYCLOPENTADIENE

Bruson and Riener

Dicyclopentadiene is formed by the dimerization of cyclopentadiene in a Diels-Alder reaction. Two structures are possible, the endo-form (I) and the exo-form (II).

I



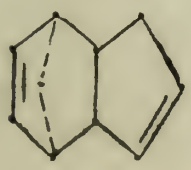
II

(All bonds in or above the plane of the paper are represented as solid lines, those below as dotted lines).

Endo-dicyclopentadiene (I) is the exclusive product of the dimerization of cyclopentadiene at ordinary temperatures. The exo-form (II) is made by heating I in a closed tube at 170°. It has not been isolated pure.

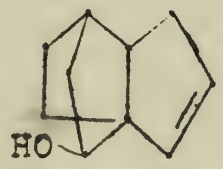
Recently, Bruson and Riener reported an addition-rearrangement reaction of I with various hydrogen donors in the presence of acid catalysts (H^+, H_2SO_4, BF_3). They proposed that a new ring system was obtained and they named it dihydro-<u>nor</u>-dicyclopentadiene.

Thus hot, dilute H_2SO_4 and I gave III or IIIa and an ether IV.



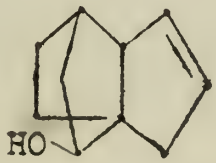
I

$\xrightarrow[H_2SO_4]{H_2O}$



III

or

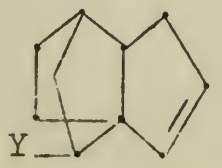


IIIa

and $(C_{10}H_{12})_2O$

IV

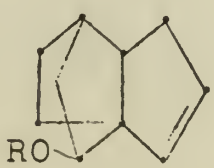
This addition-rearrangement occurred with I and halo acids in concentrated aqueous solution to give compounds of structure V (isomeric forms corresponding to IIIa are to be understood). The product from reaction of III with PCl_3 was identical with V (Y=Cl).



V.

V; Y = Cl, Br, I, not F.

VII; Y = SCH_2COOH



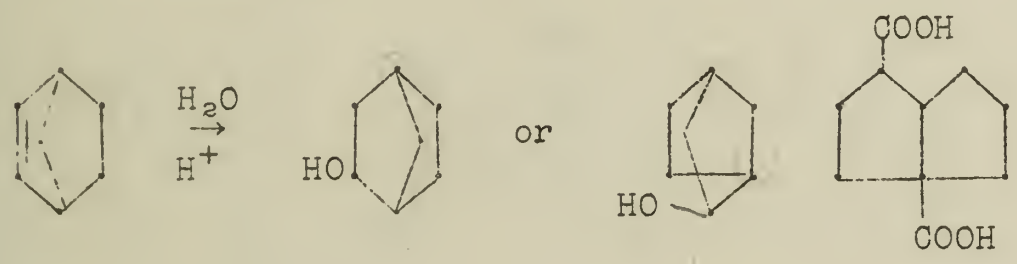
VI

Strong organic acids or weak organic acids with H_2SO_4 and BF_3 catalysts gave esters (VI, R, acetyl, benzoyl, lactyl, etc.) which could be saponified to III. Thiocyanic acid added also. Thioglycolic added but a thio-ether (VII) was formed.

Proof of Rearrangement and Structure.--The proof of rearrangement consisted in demonstrating the difference between compounds obtained from III and known compounds which have structures similar to I.

That the double bond in the 6-membered ring was the one hydrated was proved by addition of cyclopentene to cyclopentadiene to give dihydro-dicyclopentadiene (double bond in six-membered ring). Hydration of this compound gave X.

Although hydration of nor-bornylene, XIV, gave pure β-borneol (exo) on hydration, Bruson's rearrangement is still consistent with this reaction.

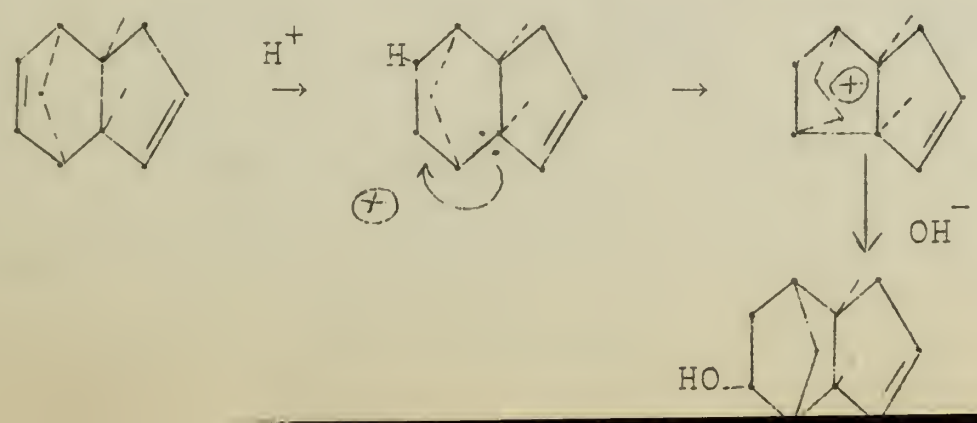


XIV XV

Oxidation of III with $KMnO_4$ or HNO_3 gave no pure compound, but X on oxidation with HNO_3 gave an acid, presumably XV.

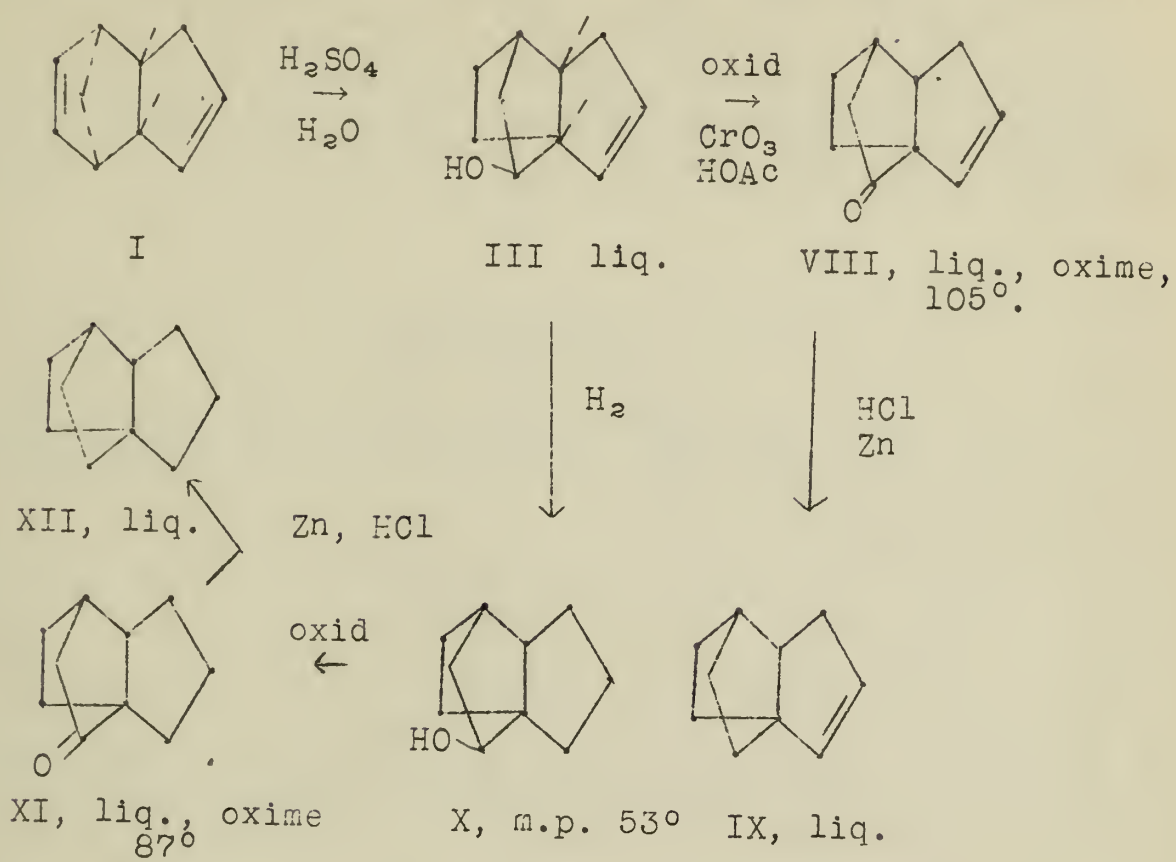
The HCl adduct (V) when treated with 10% alkali for twenty hours or with zinc and acetic acid was recovered unchanged. A Grignard reagent could be prepared. This action Bruson compares with that of neo-pentyl chloride of which V by his structure is a derivative.

Criticism of Structure.--The experimental evidence of Bruson and Riener conclusively proved rearrangement had occurred. However, Dr. Price has suggested that Bruson's structure for these compounds is unlikely on the basis of Whitmore's mechanism for rearrangements of this nature. The predicted course for the reaction on the basis of this mechanism is outlined below.

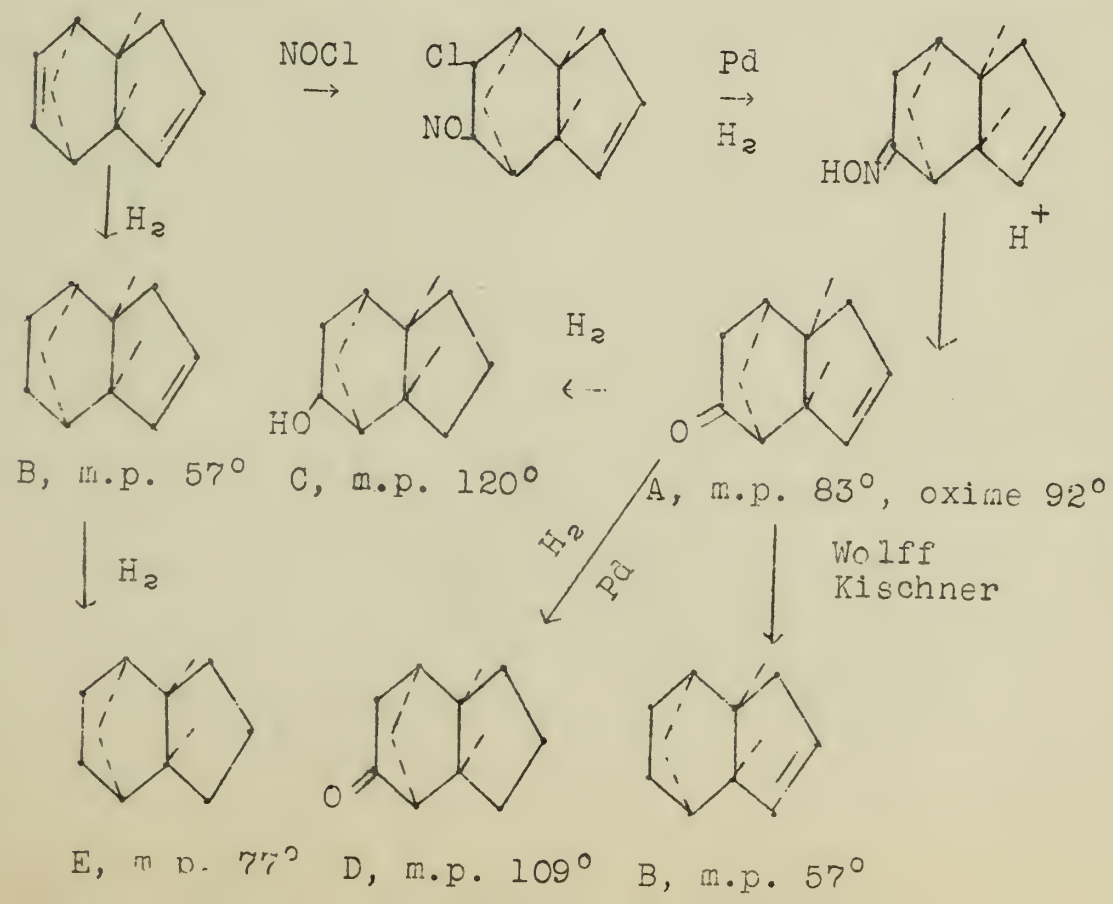


XVI

1. Reactions in rearranged series (Bruson's formulation).



2. Corresponding reactions and compounds in unrearranged series.



XVI has the methylene bridge on the same side of the 6-membered ring as the cyclopentene ring (exo-form) whereas in C they are on opposite sides (endo-form). This mechanism is consistent with the hydration of nor-bornylene to β-borneol. It is also consistent with the inactivity of the chloride formed by rearrangement since bornyl chloride is relatively inactive under like conditions and the cyclopentene ring gives added hindrance.

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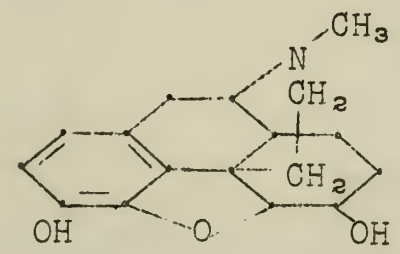
Reported by E. M. VanHeyningen
January 9, 1946

THE SYNTHESIS OF SOME COMPOUNDS STRUCTURALLY RELATED TO MORPHINE

Attempts to discover analgesics which have the excellent pain removing properties of morphine and its simple derivatives, but not the habit-forming tendencies of these drugs have led to the preparation of many compounds which have structure similarity to the parent natural product.

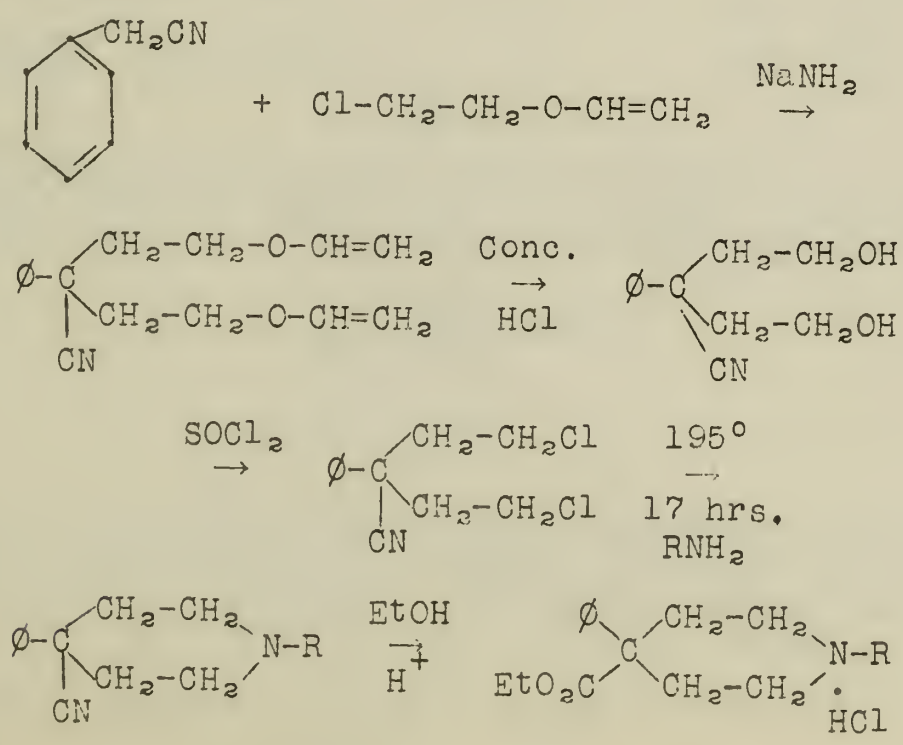
This seminar will describe the synthesis of the more recent of these analgesics as well as several recent attempts to synthesize the elusive morphine ring system (I).



I

1. Demerol (U.S.), Dolatin (Ger.), Pethidine (U.K.).--The preparation of Dolatin (II) has been described in a previous seminar by Dr. Mecorney,[1] who reviewed the work of Eisleb.[2]

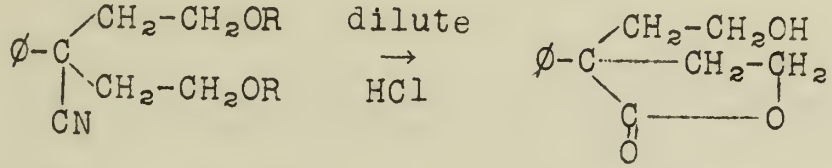
Bergel, Morrison and Rinderknecht[3a] have recently modified this synthesis to eliminate the use of the vesicant β,β'-dichloroethylmethylamine.



Pethidine, II

The 4-o-tolyl-N-methylpiperidine-4-nitrile, the corresponding acid and its ethyl ester were also prepared in this manner.

Bergel, Morrison and Rinderknecht[3b] have also examined the acid hydrolysis of α,α-bis(β'-hydroxyethyl)phenylacetonitrile under more vigorous conditions and various alkyl ethers and the cyclic ether, 4-phenylpentamethyleneoxide-4-nitrile (III). If dilute hydrochloric acid was employed, the reaction took the following course.

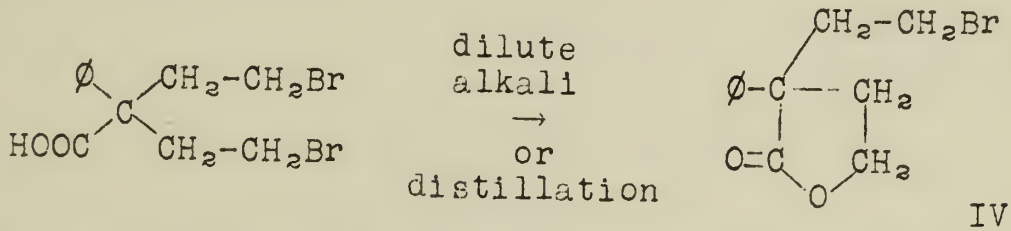


R= $-CH=CH_2$ or $-CH_2-O-CH_3$

α-(β'-hydroxyethyl)-α-phenylbutyrolactone

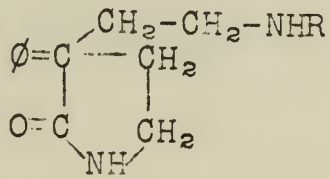
When R=Et, $CH=CH_2$, $-CH_2-o-CH_3$ and aqueous hydrogen bromide was employed, the product obtained was α-(β'-bromoethyl)-α-phenylbutyrolactone.

Walton and Green[4] have shown that, on attempted distillation of the acid (IV) or treatment with dilute alkali, a good yield of α-(β'-bromoethyl)-α-phenylbutyrolactone was obtained. When the



IV

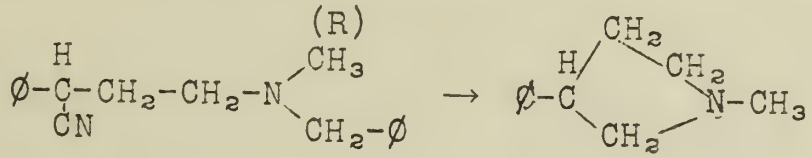
acid (IV) was esterified with either diazomethane or diazoethane, the molecule could be stabilized for further synthetic work. With ammonia, the ester gave 3-(β-aminoethyl)3-phenyl-2-pyrrolidone.



With the primary amines, such as ethylamine, n-propylamine, n-butylamine and benzylamine, however, reaction occurred normally to give a series of pethidine homologues together with smaller amounts of the corresponding lactones and lactams.

A number of other syntheses of piperidines and piperidones are reported in the literature[5,6,7,8].

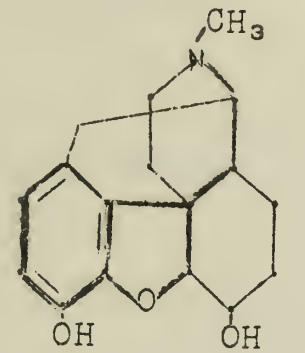
Bergel, Hindley, Morrison and Rinderknecht,[9] while attempting to prepare γ-methylamino-α-phenylbutyronitrile by selective hydrogenolysis of γ-benzylmethylamino-α-phenylbutyronitrile (V), observed that 4-phenyl-1-methylpyrrolidine was always formed.

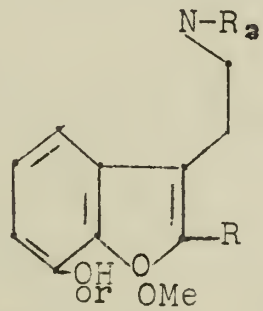


V

When R was $-CH_2-$, it was found that the second benzyl radical was removed after ring closure and secondary bases were formed.

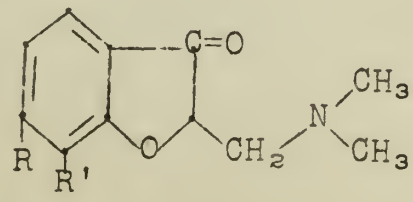
2. Benzofuran Types.--



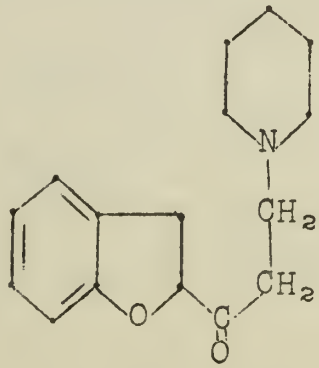


VI

Bergel, Haworth, Morrison and Rinderknecht[10] failed to prepare 3-β-dialkylaminoethylcoumarones or courmarans of type (VI), but they did prepare a 2-dialkylaminocoumaranone (VII) and a 2-β-piperidinopropionylcoumarone derivative (VIII).

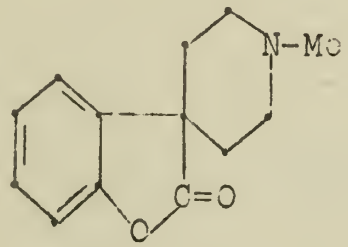


VII

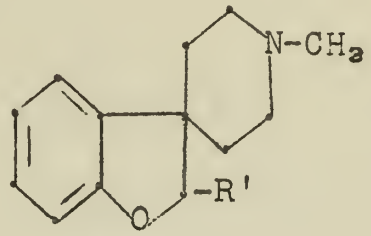


VIII

When Dolatin was announced, they extended their original work to the preparation of a coumaran of type (X), and isocoumarones of type (IX), using Eisleb's general method.



IX



X

For further interesting methods of obtaining substituted benzofuran derivatives of this type, the following references 11, 12, 13, 14, 15 are suggested.

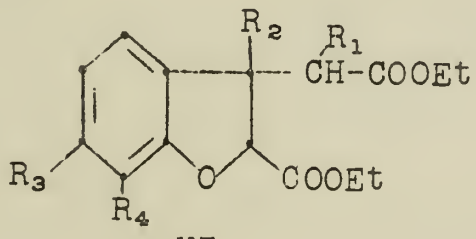
3. Isoquinoline Derivatives[16]

4. Tetrahydronaphthalene Compounds[17]

5. Dibenzofuran Derivatives[18]

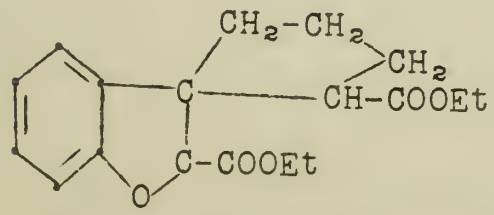
6. Attempted Synthesis of Compounds Related to Morphine Nucleus

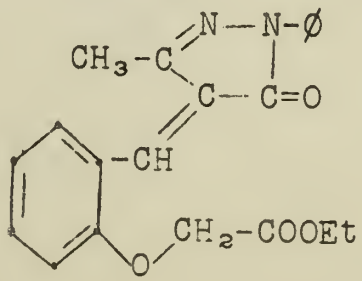
Koelsch[19] has recently investigated compounds of type (XI).



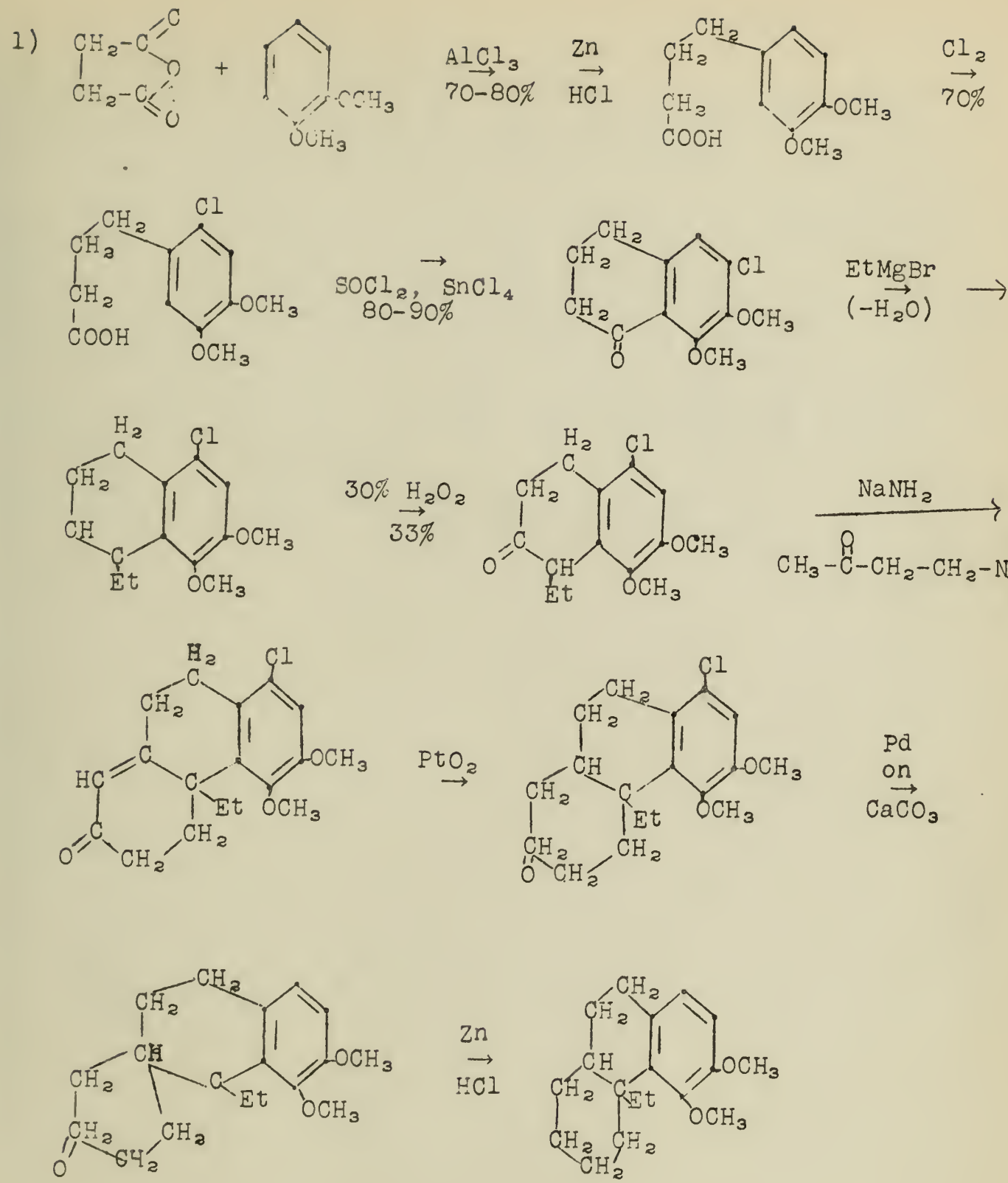
XI

Thus far he has reported the synthesis of ethyl-6-methylspiro-(coumarin-3,1'-cyclopentane)2,2'-dicarboxylate and 4-(o-carbethoxymethoxybenzal)-3-methyl-1-phenylpyrazolone-5.





Ghosh and Robinson[20] have reported the preparation of 3,4-dimethoxy-13-ethyl-5,6,7,8,9,10,13,14-octahydrophenanthrene (XII) and its 1-chloro derivative.

1) 

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Reported by C. G. Overberger
January 16, 1946.

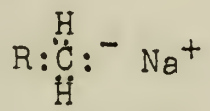
ACIDITY OF HYDROCARBONS

A. A. Morton, Massachusetts Institute of Technology

Attempting to rationalize the reactions of organoalkali compounds, Morton has based an analysis of their properties on the assumptions that they are salts of very weak acids, existing as ion-pairs in non-dissociating mediums, and that the ion-pair acts in many reactions as an electrophilic reagent because of the strong electronegativity of the cation. The second assumption appears to be unwarranted, the first is acceptable. The purpose of this seminar is to outline the evidence for the salt-like nature of organoalkali compounds and the acid properties of hydrocarbons and to review the mechanisms of a few reactions in light of this concept.

The Salt-like Nature of Organoalkali Compounds: The evidence for the salt-like nature of organoalkali compounds is threefold: the electronic formula, conductance measurements, and physical properties.

The electronic formula (I) for an alkylsodium supports the idea of an electrovalent rather than a covalent bond since both



(I)

the sodium ion and the carbon atom possess a complete octet of electrons without sharing any.

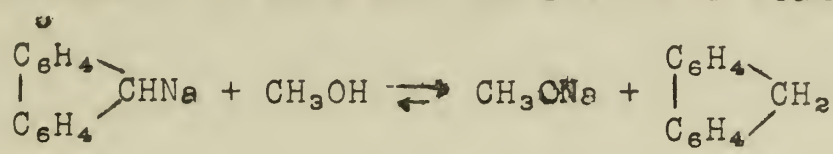
With a few exceptions the organoalkali compounds conduct an electric current in such solvents as dimethylzinc, ether, pyridine, and liquid ammonia. Since the dialectric constants of these solvents is low, the equivalent conductances are small.

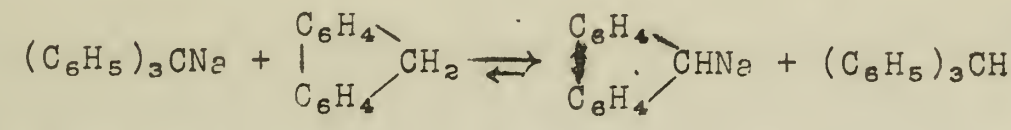
The other physical properties of these compounds vary from those of a typical salt to those of a covalent compound. For example, most of the aryl and alkyl sodium and potassium compounds are insoluble in organic solvents, are non-volatile, and, on heating, decompose without melting. On the other extreme are many of the lithium alkyls which, as might be expected from the properties of the inorganic salts of lithium, are soluble in organic solvents and sublime or distil. Between these extremes are compounds in which the metal is attached to an allyl or benzyl carbon atom. These are soluble in organic solvents but are conductors of electricity in solution.

Acidity of the Hydrocarbons: Viewing the organoalkali compounds as salts leads naturally to consideration of the hydrocarbon part of the molecule as an acid. Since the alkali metal salts of many hydrocarbons cannot be obtained by direct interaction of metal and hydrocarbon, the acidities of these hydrocarbons must be very low. An interesting problem, then, is

encountered in measuring the strengths of these weak acids.

The basis for estimating the acidities of hydrocarbons is the reaction between an acid and the salt of a weaker acid.





From the data obtained in metalation reactions under non-equilibrium conditions, a qualitative estimation of the relative acidities of a series of hydrocarbons may be made. For example, benzene, toluene, and diphenylmethane may be metalated with ethylsodium; phenylsodium will metalate toluene; and potassium amide will metalate diphenylmethane but not toluene. Thus it is concluded that the order of acid strengths is:: ethane < benzene < toluene < diphenylmethane.

A more nearly quantitative measurement of the acid strengths depends upon the determination of the equilibrium point in a substitution reaction. The acidities of the two acids are then related by the equation:

$$pK_1 - pK_2 = \log \frac{[R_1^-]}{[R_1H]} - \log \frac{[R_2^-]}{[R_2H]}$$

where K_1 and K_2 are the dissociation constants of, and R_1^- and R_2^- are the anions of the acids R_1H and R_2H, respectively. Using a variety of methods for determining the equilibrium constants, Conant and Wheland and McEwen, the latter employing methanol (pK, 16) as a reference standard, have determined the ionization constants for many amines, alcohols and hydrocarbons.

In many cases the constants found by the above method serve as reference standards and allow amplification of the series by the cruder qualitative method. Morton has arranged some typical hydrocarbons in the following order of increasing acidity:

Compound	pKa
Alkane (tertiary)	<37
Alkane (secondary)	<37
Alkane (primary)	<37
Methane	<37
Benzene	<37
Toluene----------	near 37

Compound	pKa
Diphenylmethane---------	35
Triphenylmethane--------	33
Xanthene----------	29
(Aniline----------	27)
Fluorene----------	25
Phenylacetylene---------	21

In general it has been found that substitution with electropositive groups on carbon by alkylation, chain-lengthening, or chain branching-decreases the acidity of the hydrogen bound to it. Conversely electronegative groups such as phenyl, vinyl, nitro, and carbonyl attached to a carbon atom increase the acidity of the hydrogen attached to that atom. Ethereal oxygen appears to increase the acidity. Parallel effects on acidity can be noted in substitution in carboxylic acids, alcohols, and amines.

Reactions: (1). Substitution. The substitution reaction, involving the reaction of a salt of weak acid with a stronger acid to form the weak acid and the salt of the stronger acid has been illustrated in the discussion of the estimation of acid strengths. In this reaction the potassium salt of a given hydrocarbo acid is more reactive than the sodium salt, which, in turn, is more reactive than the lithium salt. According to Morton this is evidence for the theory that the cation plays the dominant role in the reaction. It seems more reasonable, however, to relate this effect to the increased basicity of the anion as the cation is changed from lithium, with a gaseous ionization potential of 5.36 volts, to potassium, with an ionization potential of 4.32 volts.

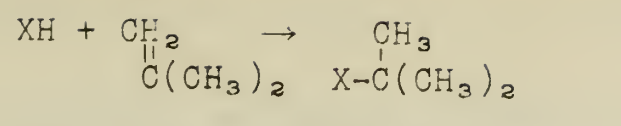
Morton (1945) has used the substitution reaction in the preparation of β,γ-unsaturated acids by metalating olefins with amylpotassium or amylsodium and carbonating the resulting salt. In this fashion β-methylvinylacetic acid was prepared from isobutene, and vinylacetic acid was prepared from propene. A mixture of α,β- and β,γ-unsaturated acids was obtained from 1-pentene. The yields in these reactions are not high.

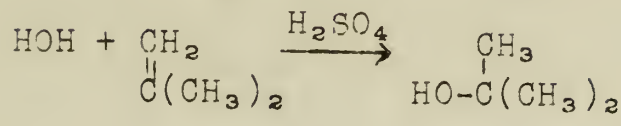
(2) Disproportionation Reactions. The reaction between an organic halide and an organoalkali compound to produce an olefin derived from the halide and an alkane derived from the salt is viewed by Morton as involving attack on the halogen by the cation. There seems to be little reason, however, for postulating this mechanism in favor of the one commonly accepted for the action of bases on halides:

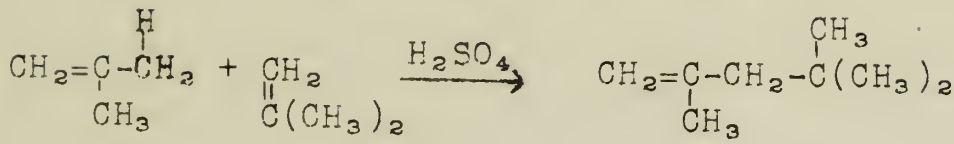
$$R\text{-}CH_2\text{-}CH_2\text{-}Cl + R':^- \rightarrow R\text{-}C\overset{\ddot{}}{H}\text{-}CH_2\text{-}Cl + R'H$$

$$R\text{-}CH = CH_2 + Cl^-$$

(3) Addition of Olefins. According to Morton (1945) the dimerization of olefins and the addition of one olefin to another under acid catalysis may proceed in a fashion analogous to the addition of water and acids to double bonds, with the adding olefin reacting as a weak acid. The dimerization of isobutene is an example.

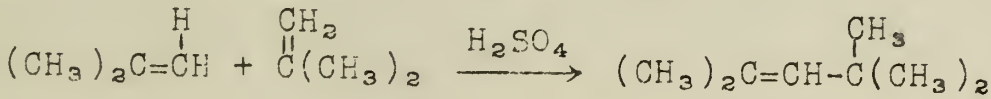






(II)

It is postulated that the stronger the acid the easier the addition. The dimer (III) resulting from the addition of the very weakly acid methylene group should, then, be the minor product.



(III)

It is found that (II) and (III) are formed in the ratio of four to one.

In some cases the course of the reaction is altered from that expected by the influence of the catalyst on the relative acidities of the various hydrogens and by rearrangement of the expected products.

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Reported by D. A. Shepherd
January 16, 1946

THE USE OF HEXAMINE IN THE FORMATION OF AROMATIC ALDEHYDES

From Alkyl Halides. Hexamethylenetetramine or hexamine behaves toward alkyl halides as a tertiary base giving relatively unstable addition complexes of the form $C_6H_{12}N_4 \cdot RX$. Sommelet showed that the complexes formed with benzyl halides were decomposed by boiling water into aldehydes. Thus from the addition complex of benzyl chloride and hexamine there was obtained a 70 per cent yield of benzaldehyde. A mixture of bases is also produced--methylamine, dimethylamine, trimethylamine, benzylamine, and ammonia--but the aldehyde is the only neutral product formed. Sommelet also carried out the reaction with o-, m-, and p-toluyl bromides which gave good yields of the corresponding aldehydes.

The mechanism he suggested presumed initially the formation of methylenebenzylamine followed by rearrangement of the latter to benzylidenemethylamine which should undergo hydrolysis readily to form benzaldehyde.

$$C_6H_5CH_2N{=}CH_2 \rightarrow C_6H_5CH{=}NCH_3 \rightarrow C_6H_5CHO + CH_3NH_2$$

From Amines. The work of Graymore and Davies has substantiated this mechanism by showing that methylenebenzylamine, as well as the crude product of the reaction of formaldehyde with benzylamine, could be converted in the presence of hexamine to benzaldehyde.

$$C_6H_5CH_2N{=}CH_2 + HCl \text{ (to dissolve)} \xrightarrow[H_2O]{\text{hexamine}} C_6H_5CHO \qquad 60\%$$

In the absence of hexamine no aldehyde is formed. Perhaps the hexamine is necessary to catalyze the prototropic rearrangement, since Ingold has found that alkali fusion of methylenebenzylamine brings about 10 per cent conversion to benzylidenemethylamine. The low yield here is probably due to polymerization of $C_6H_5CH_2N{=}CH_2$ to tribenzyltrimethylenetriamine in the presence of alkali so that isomerization is precluded.

Graymore and Davies conclude that methylenebenzylamine is formed initially by the hydrolysis of the benzyl chloride-hexamine complex. If conditions are unfavorable for extensive polymerization, isomerization to benzylidenemethylamine occurs. By interaction of the latter compound with aminomethanol (from hexamine) benzaldehyde is produced.

$$C_6H_5CH{=}NCH_3 + H_2O + NH_2CH_2OH \rightarrow C_6H_5CHO + CH_3NHCH_2OH + NH_3$$

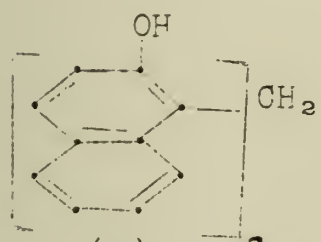
Copious evolution of ammonia is noted.

The o-, m-, and p-chlorobenzylamines were converted to the aldehydes in yields of 38, 50 and 50 percent, respectively; α-phenylethylamine gave 30 percent yield of acetophenone.

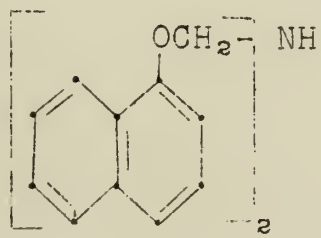
From Phenols. A different method of preparing aromatic aldehydes from hexamine is that of Duff which grew out of his

observation that heating an aqueous solution of salicylic acid and hexamine gave a mixture of the 3- and 5-formyl derivatives. A study of this reaction using the naphthols yielded the results in the following table.

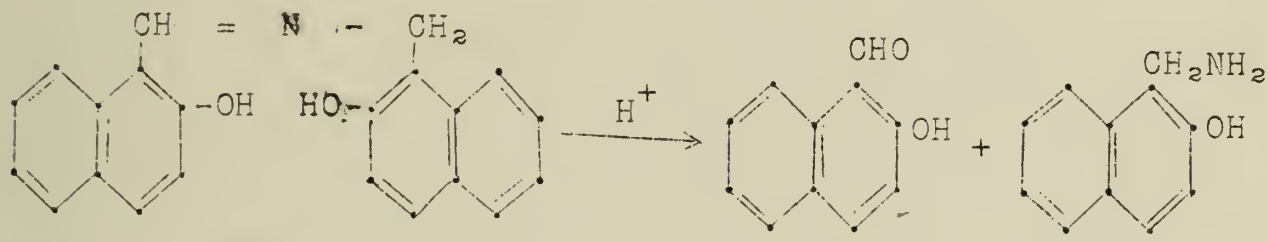
	α-naphthol	β-naphthol
aq. alcoholic solution	complex amorphous product	bis(2-hydroxy-1-naphthyl)methane (I)
acetic acid solution	bis(1-naphthoxymethyl)amine (II)	2,2'-dihydroxy-1-naphthylidene-1'-naphthylmethylamine (III)



(I)



(II)



(III) (IV) (V)

Compound III is hydrolyzed by dilute acid to the aldehyde IV and the amine V; this constitutes a convenient preparative method for these materials.

From these experiments was evolved a method for the formylation of phenols which can compete with the Reimer-Tiemann reaction. The phenol and hexamine are heated together at 150-160° in a solution of glyceroboric acid in anhydrous glycerol. The product is obtained from the reaction mixture by steam distillation. The advantages of this method over the Reimer Tiemann procedure are that it is quicker, sometimes gives better yields, does not require separation of the aldehyde as the bisulfite addition product since no phenol is left unchanged and gives exclusively <u>ortho</u> substitution.

The mechanism proposed is similar to that for the Sommelet reaction.

$$3RH + C_6H_{12}N_4 \rightarrow NH_3 + 3RCH_2N{=}CH_2 \rightarrow RCH{=}NCH_3 \rightarrow RCHO + CH_3NH_2$$

(RH = a phenol)

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Reported by Robert A. Bauman
January 23, 1946

SEMINAR TOPICS

II Semester 1945-46

Cyclooctatetraene

The constitution of the hydrocarbon C_8H_8, obtained by polymerization of acetylene, has been "definitely determined", according to Reppe, as cyclooctatetraene. The processes of obtaining cyclopolyenes from acetylene have been carried out only on a laboratory scale. A single pilot plant run for thirty days was attempted but was not successful. For the preparation of C_8H_8, or cyclooctatetraene, in the laboratory, the following conditions were observed.

The solvent was tetrahydrofuran, kept anhydrous by the addition of calcium carbide powder (50g./2l.). The catalyst was nickel cyanide (20g.), which was found to be singularly effective for conversion of acetylene with comparatively little benzene and resin formation. The catalyst was made as follows: nickel chloride was dissolved in denatured alcohol, the solution was cooled to 0-10° and was then treated with a ca. 10% solution of HCN in alcohol. The solution was allowed to stand for twelve hours at this temperature, treated again with alcoholic HCN solution to complete precipitation, and after standing another twelve hours, the precipitated nickel cyanide was collected on a filter. The light blue nickel cyanide was washed with water until neutral and was then converted to the yellow-brown anhydrous salt by heating at 175°. Other nickel cyanide was inferior in effectiveness to the salt produced in this way. Other nickel salts were unsatisfactory.

The solvent, containing calcium carbide and the nickel cyanide catalyst, was placed in a 4 or 5 liter autoclave and the apparatus was purged of air by means of a nitrogen stream. Under a nitrogen pressure of 5 atmospheres, the inside temperature of the autoclave was raised to 60-70°. The contents were kept in motion by agitation or rolling. Acetylene was introduced until the pressure rose to 15-20 atm., and subsequent additions of acetylene were made hourly to maintain this pressure. When the reaction was stopped after 60 hours, a brown solution was obtained. The suspended cuprene and catalyst were removed by filtration and the filtrate was given a preliminary distillation at reduced pressure. When the solvent and the benzene resulting from the reaction had been removed, the residue was distilled at 14-20 mm. and the cyclooctatetraene was then subjected to rectification at atmospheric pressure. Under these conditions, 320-400g. of cyclooctatetraene were obtained, 30-50 g. of resin and approximately 50 g. of benzene.

At an operating temperature of 60-70°, C_8H_8 was obtained as a golden yellow liquid, b.p. 142-143° (760), m.p. -7°. Copper powder and higher operating temperatures were shown to be effective for the formation of higher polymers, namely $C_{10}H_{10}$, deep yellow, b.p. 190-195° (760), and $C_{12}H_{12}$, bright yellow, b.p. 230-235°(760). Azulene, $C_{10}H_8$, deep blue leaflets, m.p. 99.5°, was formed as a by-product whether the operating temperature was 80° or 130°.

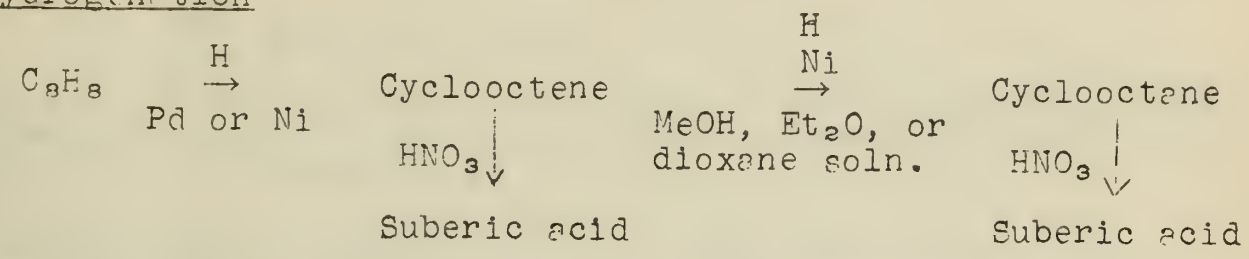
A 400 liter autoclave with auxiliary equipment was built to produce cyclooctatetraene on a larger scale. Proper operating conditions were not established during the single thirty-day run made just before the war ended; only a 2% yield was realized instead of the 90% laboratory yield. The pressure unit was 5 meters long and 45 millimeters in diameter, filled with silica get coated with nickel cyanide.

The physical properties of C_8H_8, or Reppe's cyclooctatetraene, are listed below. They are compared with those of Willstatter's cyclooctatetraene, and with those of styrene. It was pointed out in 1938 that there was a suggestively close similarity between the latter two compounds. Reppe has ignored this previous comparison in indicating the similarity between his C_8H_8 and the classical cyclooctatetraene of doubtful structure.

Property	Styrene	Willstätter's Cyclooctatetraene	Reppe's Cyclooctatetraene
b. p. (17mm.)	43°	42.2-42.4°	45.5-45.8°
m. p.	-33°	-27°	-7.4°
d_4^{20}	0.907	0.925	0.921
n_D	1.543(17°)	1.539 (20°)	1.529 (20°)
M_D^{20} found		35.20	35.17
M_D^{20} calculated			35.08
Dipole moment			0
Raman Spectrum			indicates symmetry
Heat of formation (ΔH)			40 kcal.
Heat of combustion ($-\Delta H$)			1069 kcal.
Dibromide, $C_8H_8Br_2$ m.p.	72-73°	70-71.5°	
Tribromide, $C_8H_7Br_3$ m.p.	60°	53-55°	
HBr addn. prod., C_8H_9Br b.p.	97° (17mm.)	85-87° (12.5mm.)	
Resonance energy Experimental	46 kcal.		25 kcal. (with approximation)
Calculated			18.8 kcal. (non-planar)

The chemical properties of C_8H_8 have been described in general terms in a series of reports obtained from the U.S. Department of Commerce, but full details of the chemical reactions of cyclooctatetraene and the structures and properties of its reaction products are still lacking at this time. The compound forms crystalline addition products with aqueous silver nitrate or cupric ammonia chloride and polymerizes to a dimer and hard resins on standing. It undergoes the following reactions.

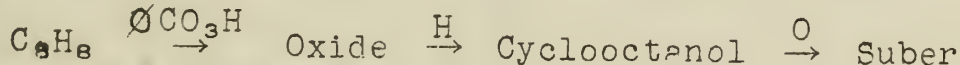
1. Hydrogenation



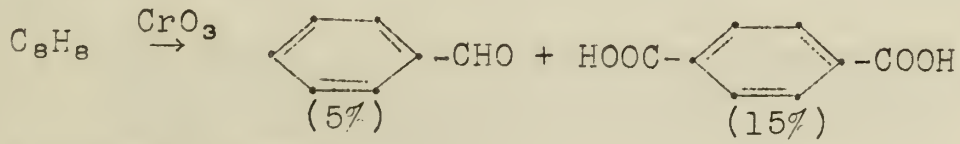
It had been pointed out previously that reduction of Willstätter's cyclooctatetraene in the presence of platinum catalyst proceeded readily to the hexahydro stage at the same rate of hydrogenation as did styrene. The fourth mole of hydrogen added more slowly to give C_8H_{16} as a liquid which melted at 6.5° in its most highly purified form. Oxidation of this product with nitric acid also gave suberic acid. The cyclooctane which Willstätter obtained by hydrogenation of his triene (from pseudopelletierine) melted at 11.6-11.8°.

2. Oxidation

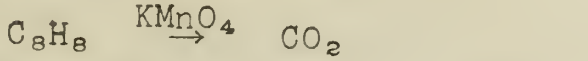
a. Air--easily oxidized in air.
b. Perbenzoic acid--



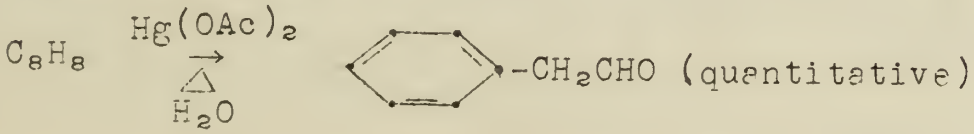
c. Chromic acid--



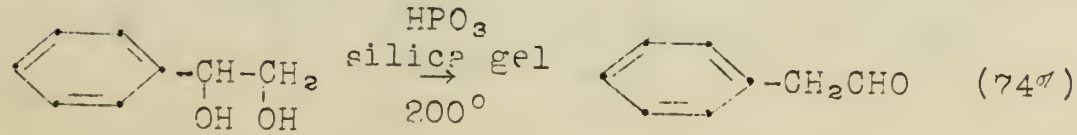
d. Potassium permanganate--



e. Mercuric acetate--



For comparison, the recent work of Emerson and Agnew is recalled



f. Hypochlorite--

$C_8H_8 \rightarrow$ OHC-  -CHO

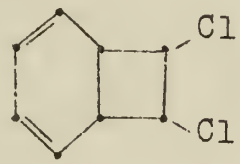
3. "Dehydrogenation"

$C_8H_8 \xrightarrow{Se}$ p-Xylene, C_8H_{10}

Previous work had shown that chromium oxide dehydrogenation of cyclooctene gave 50% styrene and 50% cyclooctane at 400° and 93% styrene and 7% cyclooctane at 450°.

4. Halogenation--Cyclooctatetraene adds one, two or three moles of chlorine or bromine, but not four.

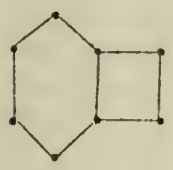
$C_8H_8 \xrightarrow{3Cl_2} C_8H_8Cl_6$, m.p. 126°

$C_8H_8 \xrightarrow[25^\circ]{SO_2Cl_2 \text{ in } CHCl_3 \text{ or } CCl_4} C_8H_8Cl_2$, 

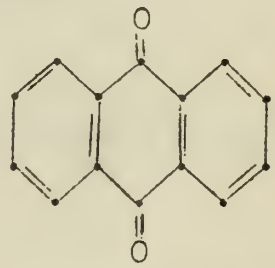
Reactions of $C_8H_8Cl_2$.--

a. $C_8H_8Cl_2 \xrightarrow[Pd]{H} C_8H_{12}Cl_2 \xrightarrow[Pd]{H\ NaOH} C_8H_{14}$, m.p. 136°

Reppe showed that the product C_8H_{14} was bicyclo [4,2,0] octane,

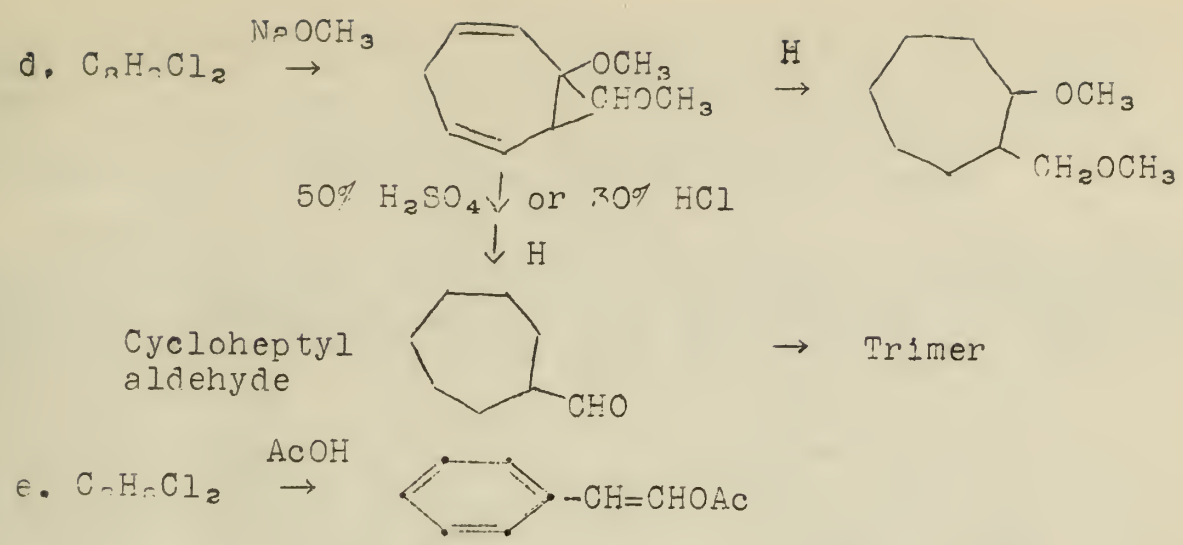


In comparison, Willstatter's dibromocyclooctadiene boiled with quinoline gave C_8H_8 which gave in turn C_8H_{14}, bicyclooctane, on hydrogenation.

b. $C_8H_8Cl_2 \xrightarrow{\text{Naphthoquinone}}$ Addition product $\xrightarrow{\Delta}$ 

Anthraquinone

c. $C_8H_8Cl_2 \xrightarrow{CH_3OH}$  $-CH(OCH_3)-CH_2OCH_3$ + 2HCl



Reactions a through e were described as proceeding in 60% yield or better.

From this description of the physical and chemical properties of Reppe's C_8H_8, it will be seen that there is some evidence of the cyclooctatetraene structure. Information available at present on this chemistry is not sufficiently detailed, complete, or convincing to merit unreserved acceptance of C_8H_8 as 1,3,5,7-cyclooctatetraene. However, with such a pioneer compound one might expect such frontier chemistry as is indicated by the retaining of the eight-carbon ring structure, the conversion to the aromatic series, and the apparent conversion to the bicyclo [4,2,0] octane ring system.

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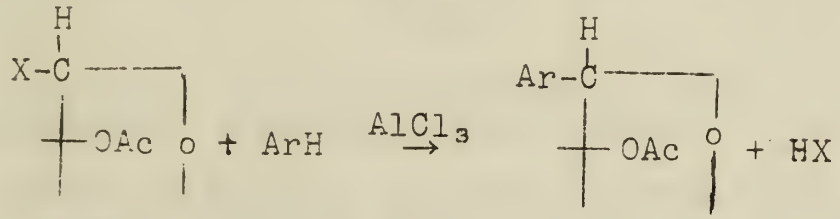
Nelson J. Leonard
March 6, 1946

THE ARYLATION OF SUGARS

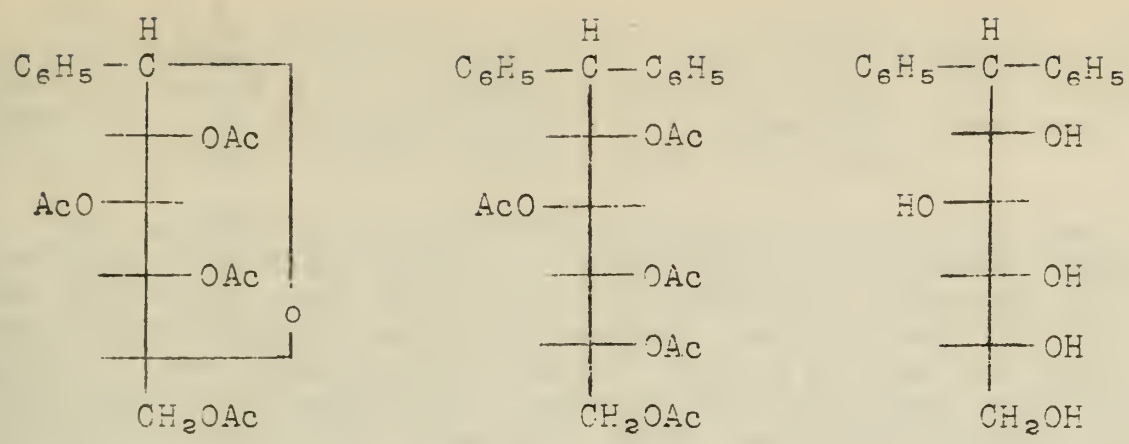
Until the present investigation by Hurd and coworkers (1), aluminum chloride was not used extensively in carbohydrate chemistry. Much of the previous work by Von Arlt (2), Skraup and Kremens (3), Hudson and Johnson (4), Braun (5), and Kunz (6) dealt with the formation of the glycosyl chlorides and the inversions that occurred under the conditions used.

Recently Hurd investigated the reaction between hemiacetal halides and aromatic hydrocarbons in order to ascertain whether they would undergo Friedel-Crafts type reactions. Neglecting possible ester reaction, the expected equation is:



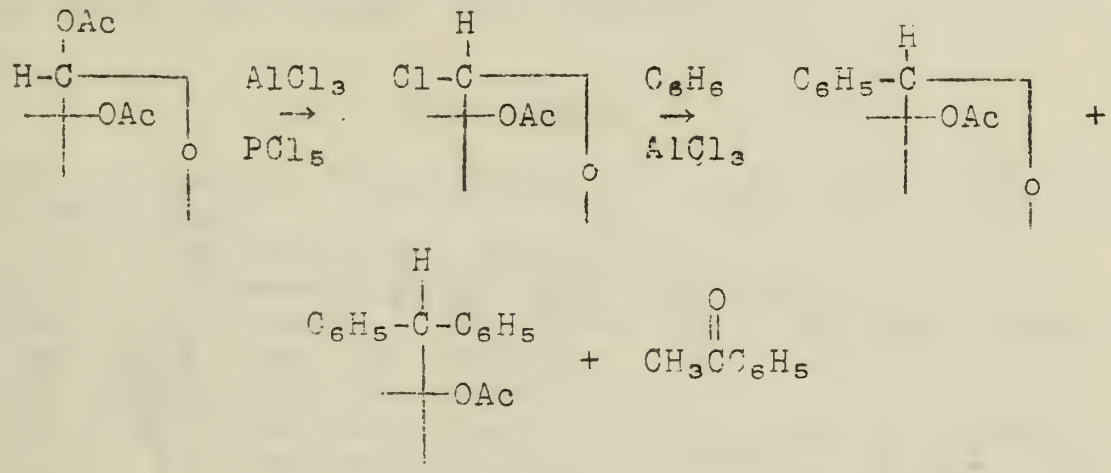
When catalytic amounts of aluminum chloride and tetra-acetyl-α-glucosyl chloride were used, starting material was invariably recovered. The presence of a sweet odor, however, indicated that the ester function had undergone some reaction, in all probability yielding acetophenone. This is plausible since other investigators (7) have found that esters and aromatic hydrocarbons in the presence of aluminum chloride yield alkyl, aryl, or acyl derivatives depending upon the conditions employed.

Since two moles of aluminum chloride are necessary to react with each ester group, a total of nine moles would be necessary to bring about reaction of the chloride function. Actually it was found that five moles were sufficient. Upon working up the reaction mixture the anticipated acetophenone was found in the benzene layer and a sirupy residue in the water layer. The sirupy residue was acetylated to yield a crystalline derivative (I) whose structure was proven by analytical data and oxidation to benzoic acid. In an attempt to increase the yield eight moles of aluminum chloride were employed and a second compound (II) was isolated which upon deacetylation gave (III). (III) could be obtained if the residue from the reaction was not acetylated first. Oxidation to benzophenone and analytical data again substantiated the proposed formulas. Extensions of the reaction to toluene yielded analagous products; methyl p-tolyl ketone and two corresponding carbohydrate derivatives, both of which were proven by oxidation. With naphthalene only the methyl naphthyl ketone was isolated, the sugar compound being non-identifiable.

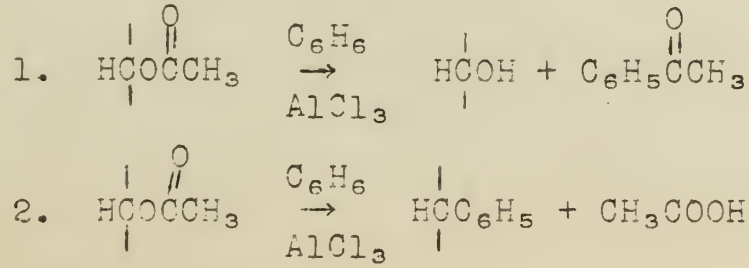


(I) Tetraacetylglucopyranosylbenzene (II) 1,1-Diphenyl-1-desoxyglucopentaacetate (III) 1,1-Diphenyl-D-glucitol

Glycosylation of benzene and other hydrocarbons by the pentaacetates seemed probable since earlier investigators had shown that chlorides were formed by the acetylated sugars in the presence of aluminum chloride and phosphorus pentachloride. The expected reaction would be the following:



This was actually accomplished although the yields were not as good as those obtained from the pyranosyl chlorides themselves. Due to the greater availability of the pentaacetates a series of reactions were run to determine what ratio of aluminum chloride would yield the best results. The theoretical amount gave the best yields. In the experiments, a goodly portion of tar was isolated. This is explainable because of the two competing reactions, acylation and alkylation, possible at the ester function:



The first explains formation of acetophenone and yields a stereochemically intact residue. The second involves rupture of a bond attached to an asymmetric carbon atom. This would lead to products of varying degrees of optical activity and of high molecular weight--both of which were obtained.

Throughout, in naming his products, the author assumed retention of configuration. In an attempt to prove this, the same compounds were synthesized by means of Grignard reagents. Several previous attempts to prepare derivatives (8, 9) of sugars by the Grignard method had failed or led to the isolation of the expected carbinol. Recognizing, however, that reaction occurred at the ester function, Hurd employed twelve moles of the phenylmagnesium bromide to one of tetraacetylglucosyl chloride. The carbinol and glucosylated benzene were isolated. A mixed melting point showed the benzene derivatives from the Friedel-Crafts and Grignard reactions to be the same. A further outgrowth of the Grignard reaction is that it appears to be the ideal way of making the mono-substituted sugar derivatives, since the reaction is cleaner, gives greater yield, is much quicker, and much more versatile. Furthermore, since the Grignard reagent introduces only one group, it is possible to prepare mixed substituted sugar derivatives.

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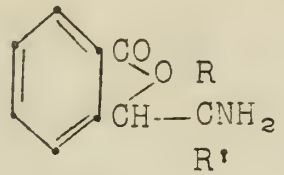
Reported by L. Katz
March 20, 1946

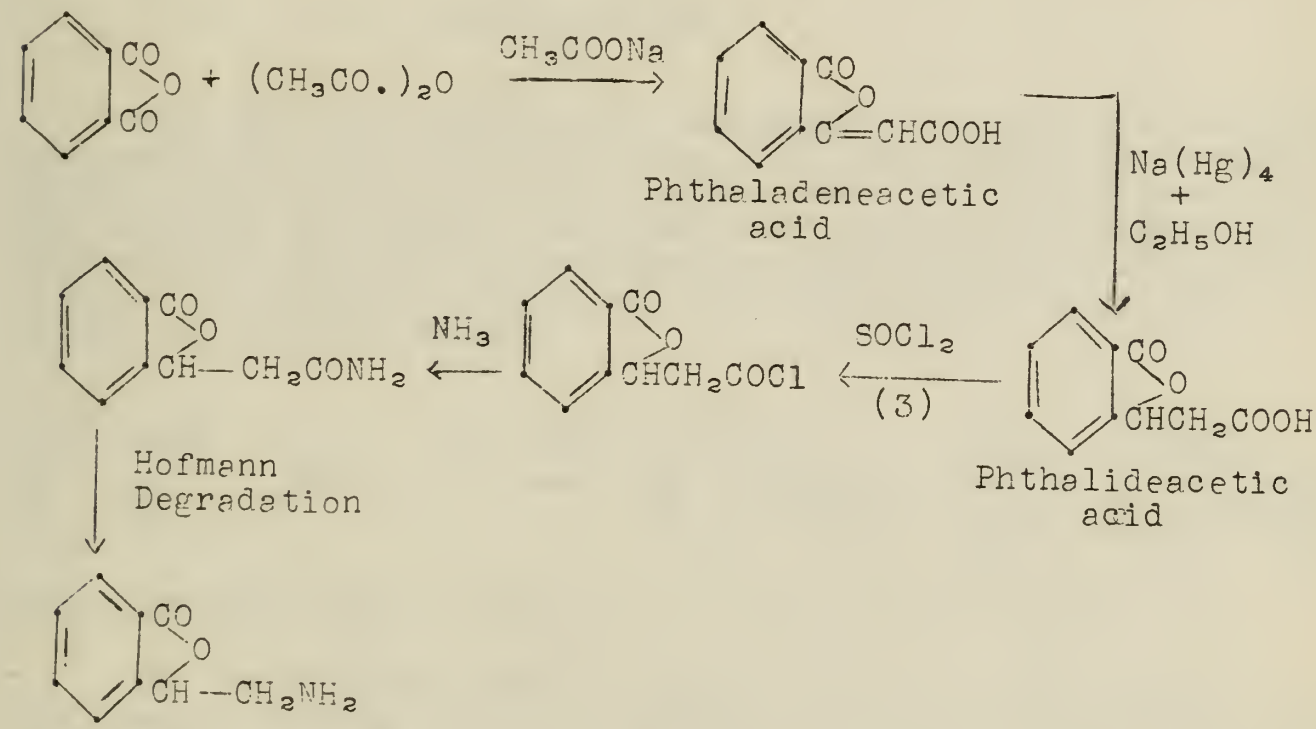
PHTHALADON AND RELATED COMPOUNDS

The "phthaladon compounds" (aminophthalidealkanes) are compounds which have the following general structure:



These compounds all contain the β-phenylethylamino grouping which is common to pharmaceuticals possessing vasopressor action and they are also esters of benzyl alcohol,. which is known to contribute to the anesthetic effect.

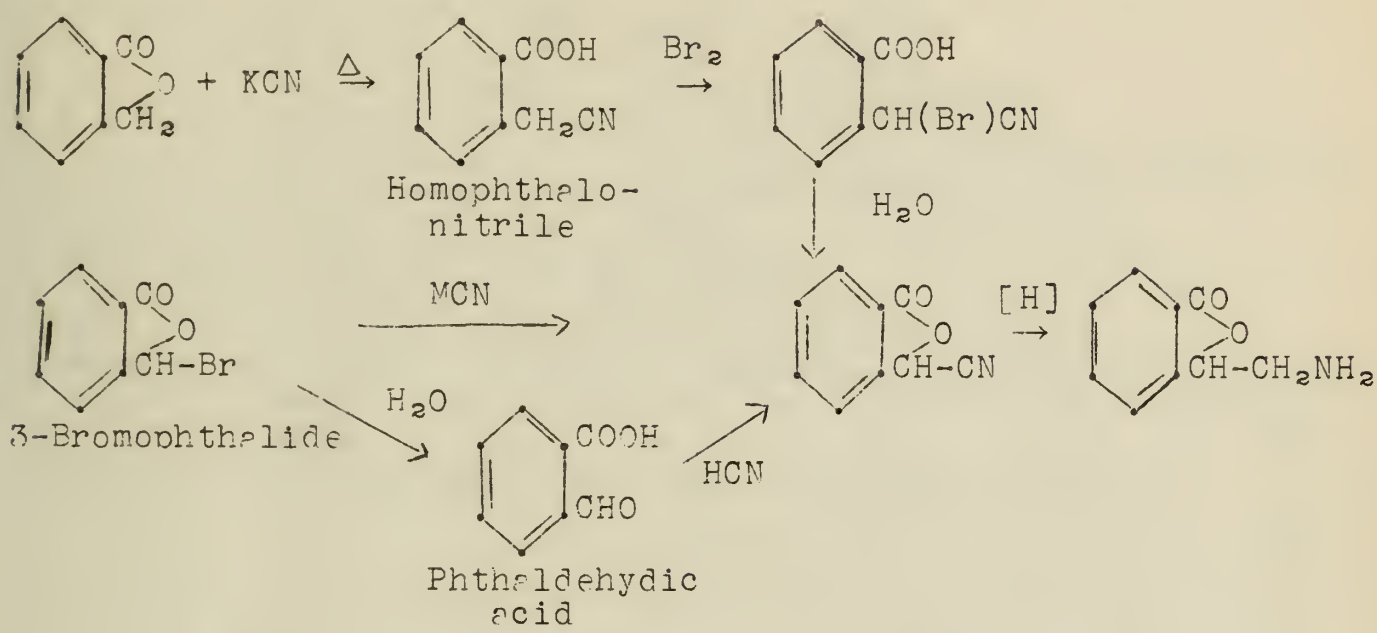
Compounds of this type were made by the Hofmann degradation of the corresponding phthalideacetamides (1,2). Their synthesis is outlined by the following series of reactions:



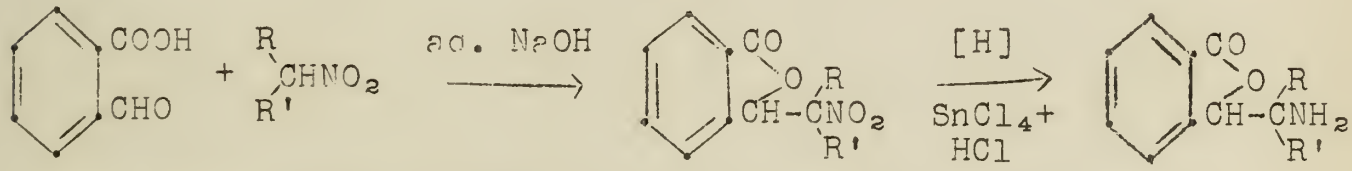
This series of reactions gave such low yields that other methods of synthesis were investigated.

Phthalideacetic acid can be made by several other methods: i.e., the condensation of phthalic acid and malonic ester followed by hydrolysis and decarboxylation (4,5,6); by the condensation of phthalide with diethyl oxalate followed by reduction and hydrolysis (7); and by the condensation of phthaldehydic acid with acetone followed by hypochlorite oxidation of the resultant methyl ketone (8).

Several other methods of synthesis which were found to be impractical are given below:



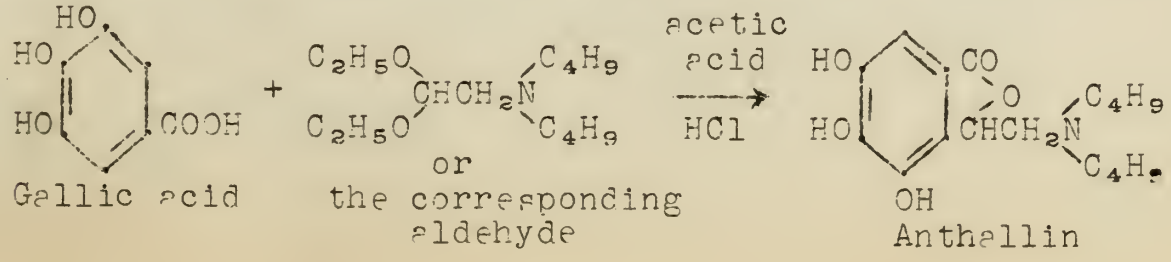
Rodionow (9) reported the condensation of opianic acid with nitromethane. Dey and Srinivasan (10) made phthalidenitromethane, by the condensation of phthaldehydic acid and nitromethane in the presence of sodium methoxide, and reduced the condensation product with zinc and hydrochloric acid. These methods led to a general method for producing phthalideaminoalkanes. This method is outlined below:



Phthaldehydic acid was made by the method of Racine (11).

The N,N-dialkylamides of phthalideacetic acid possess analgesic activity but this activity is less than that of aspirin or morphine. The phthalidealkylamines have little appreciable pressor effect. 1-Phthalide-1-aminopropane had the highest analgesic effect combined with the lowest toxicity of the primary amines studied (12).

Just recently a compound of the phthaladon type which possesses very good pressor action has been reported (13).



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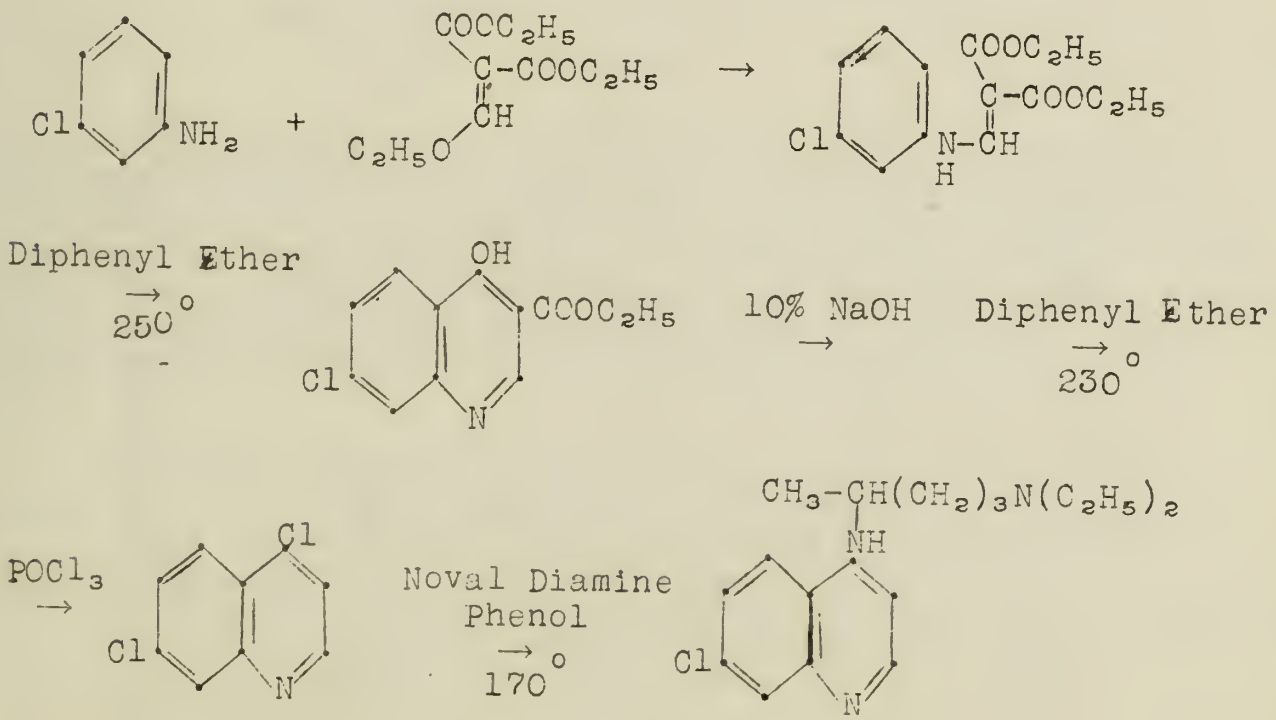
Reported by F. E. Boettner
March 20, 1946

Synthesis of Antimalarial Drugs

It is the purpose of this seminar to describe some work on the synthesis of antimalarials done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Illinois.

In 1937 Andersag, Breitner, and Jung of I. G. Farbenindustrie synthesized certain 4-dialkylaminoalkylaminoquinoline derivatives and found that these compounds had a marked physiological activity as malarial therapeutics. In the series of reactions leading to the final synthesis of these quinoline derivatives, 4-hydroxyquinolines were important intermediates. Since the methods of Andersag, Breitner, and Jung were of limited value in producing the intermediate 4-hydroxyquinolines, a more satisfactory synthesis was sought.

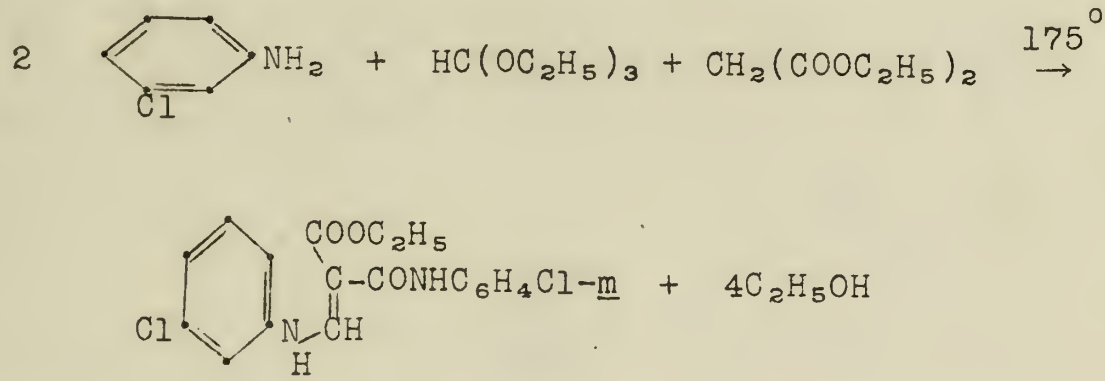
It had been shown that aromatic amines could react with ethoxymethylenemalonic ester to form α-carbethoxy-β-anilinoacrylates which then might be cyclized to 3-carbethoxy-4-hydroxyquinolines. In this way m-chloroaniline was transformed to 3-carbethoxy-4-hydroxyquinoline. Hydrolysis of the ester group, decarboxylation, and replacement of the 4-hydroxy group by chlorine through the use of $POCl_3$ yielded 4,7-dichloroquinoline. This could then be condensed with noval diamine (4-amino-1-diethylaminopentane) to form 7-chloro-4-(4-diethylamino-1-methylbutylamino) quinoline or as designated by the Survey of Antimalarial Drugs of the National Research Council, SN-7618.



This drug which is administered as the diphosphate has excellent suppressive properties and produces none of the disagreeable effects of nausea, cramps, and yellow discoloration of the skin often caused by atebrine.

Although the yields obtained in the ethoxymethylenemalonic ester synthesis were excellent, attempts were made to improve the synthesis by various simplifications. A number of modifications, therefore, were investigated.

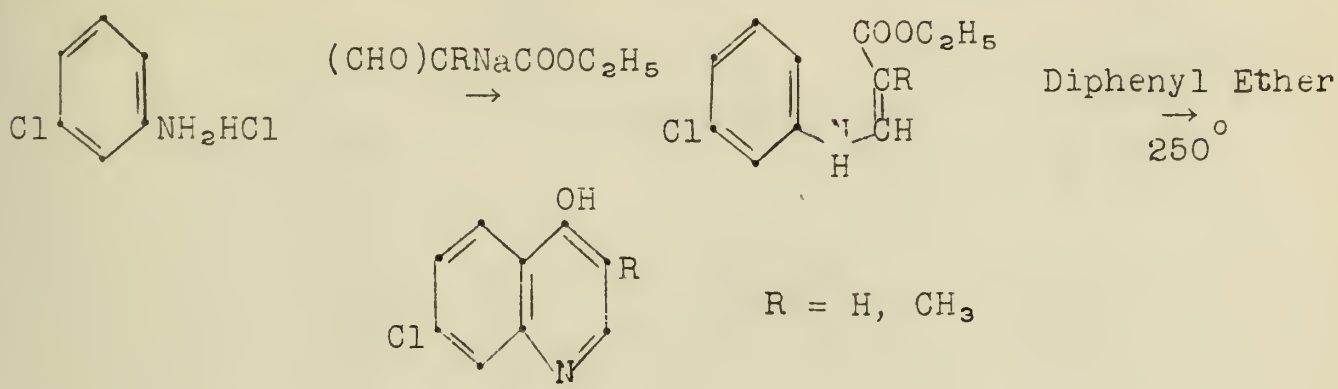
One such variation involved heating a three-component mixture of m-chloroaniline, orthoformic ester, and malonic ester at 175° with the hope of obtaining α-carbethoxy-β-(m-chloroanilino)-acrylate. This possible short-cut was suggested by the fact that ethoxymethylenemalonic ester was prepared from orthoformic ester and malonic ester. Unfortunately, the desired acrylate was not obtained as such but rather in the process one ester group was replaced by a m-chloroanilide group to form the corresponding half anilide.



In the same manner α-cyano-β-(m-chloroanilino)acrylate was formed by substituting cyanoacetic ester for malonic ester. Although both these acrylates were cyclized successfully, the cyano derivative underwent this transformation in good yield only when a large amount of diluent was employed. The 3-cyano- and 3-carbanilido-quinolines formed may be converted to the corresponding 3-carboxy-7-chloro-4-hydroxyquinoline by acid hydrolysis.

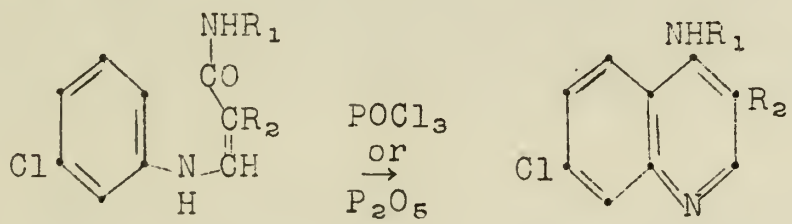
A desired simplification of the synthesis of 4-chloroquinolines was to be found by using β-anilinoacrylates unsubstituted by a carbethoxy group, for this would eliminate the intermediate operations of hydrolysis and decarboxylation. This was accomplished by the condensation of anilines with formylactic ester. However, several serious drawbacks have been encountered in this series. First, the acrylate could be formed in but low yield (25-35 per cent). Secondly, the cyclization was successful only if carried out in high dilution. In more concentrated volumes a great deal of tarry material was obtained, as well as symetrical urea derivatives. Corresponding α-methyl-β-anilinoacrylates could be prepared from α-formylpropionic ester and the

appropriate aromatic amines. In this case cyclization was satisfactory, even when less diluent was used, yields being about 80 per cent.



Although the practical implications of these syntheses are limited, they are sometimes quite useful in making research quantities when other methods fail.

An interesting direct synthesis of alkylaminoquinolines themselves utilized substituted amides of anilinoacrylates which could be cyclized in boiling xylene in the presence of phosphorous oxychloride or phosphorous pentachloride.



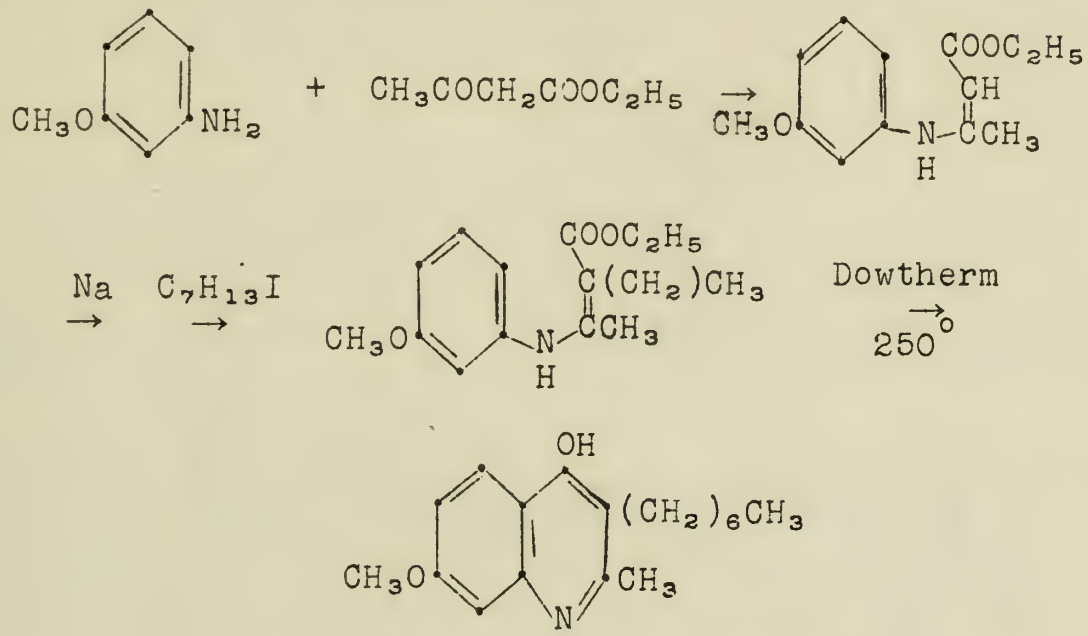
R_1 = C_6H_5, n-Bu, n-Hex, $CN(CH_2)_5$

R_2 = $COOC_2H_5$, CN

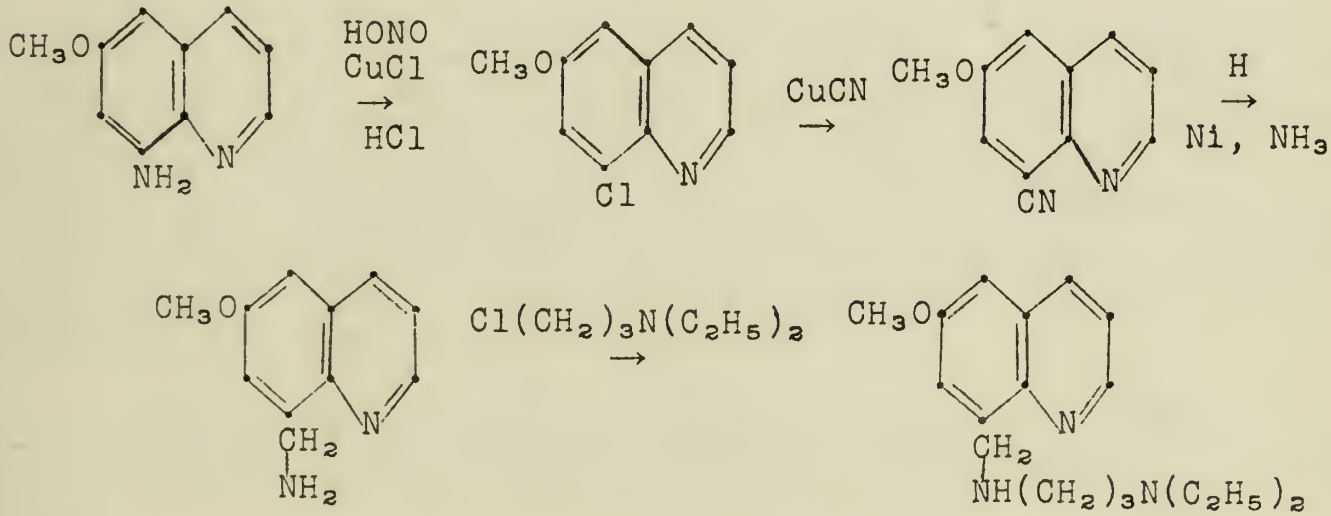
A number of 4-chloroquinoline derivatives which have been condensed with dialkylaminoalkylamino side chains have been prepared. These include 4-chloro-6-fluoroquinoline, 4-chloro-7-fluoroquinoline, 4-chloro-7-trifluoromethylquinoline, 4,7-dichloro-1,10-phenanthroline, 7-chloro-1,10-phenanthroline, 4,7-dichloro-6-methoxyquinoline, 4,7-dichloro-5-methoxyquinoline, and 6,6'-bis-4-chloroquinolyl sulfoxide.

An interesting class of antimalarials, studied in Germany during the war, which contained no basic side chain, was the 2,3-dialkyl-4-quinolinols. The derivative of this series to attract the most attention was 3-heptyl-7-methoxy-2-methyl-4-quinolinol which was called endochin. This drug was found to be an excellent prophylactic in avian malaria. Unfortunately, however, this prophylactic action has not been observed in human subjects in limited

clinical tests. Since, however, further investigation seemed warranted and detailed information for the preparation of the compound was not at hand, a synthesis was devised.



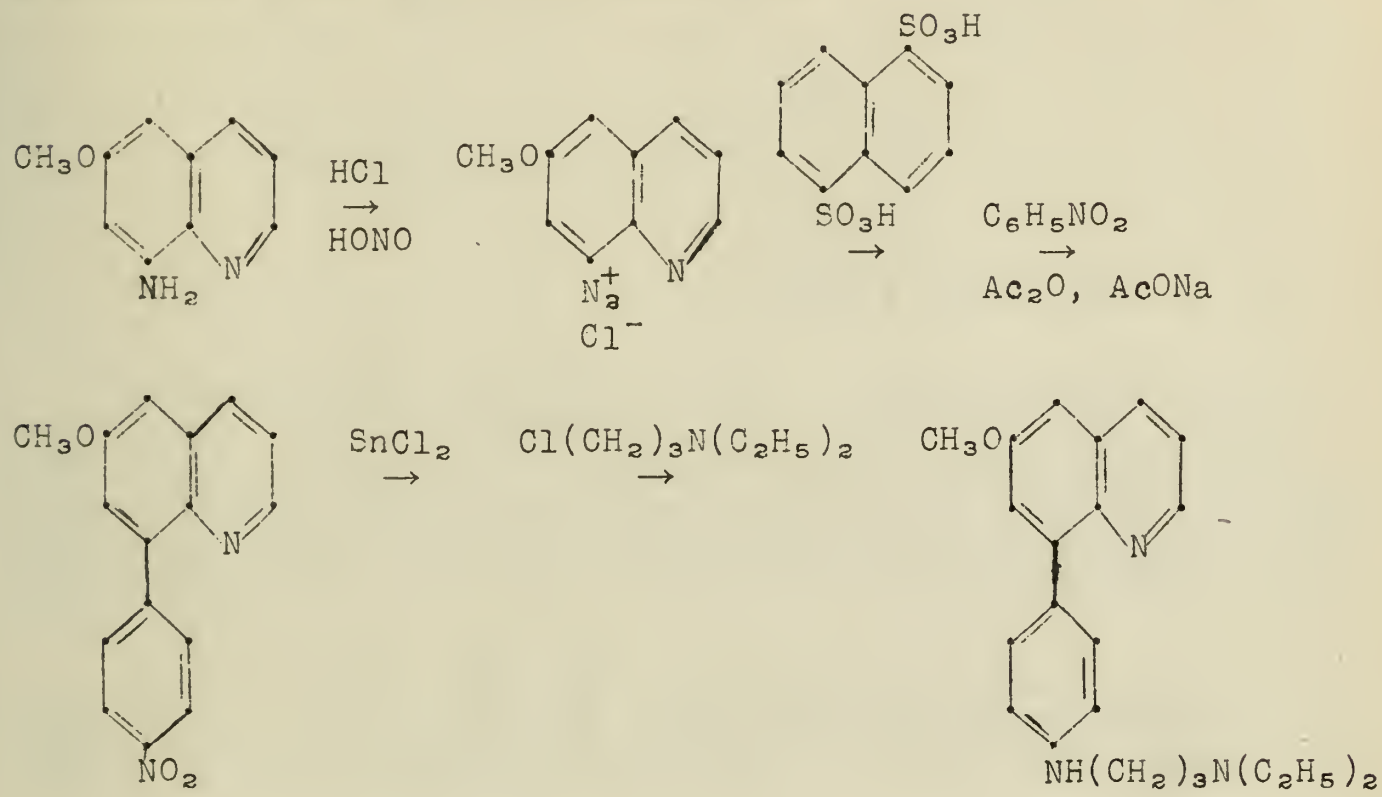
Certain plasmochin homologs were synthesized in the hope of reducing toxicity without substantially reducing the activity. The preparation of one such homolog involved the introduction of a methylene group between the basic side-chain and the nucleus, as follows:



8-Amino-6-methoxyquinoline was converted to 8-chloro-6-methoxyquinoline by diazotization. The 8-chlorine was then replaced by a cyano group by a Rosenmund-von Braun reaction. The cyano group was hydrogenated to the aminomethyl group, in the presence of Raney nickel and ammonia. The alkylation of the amino

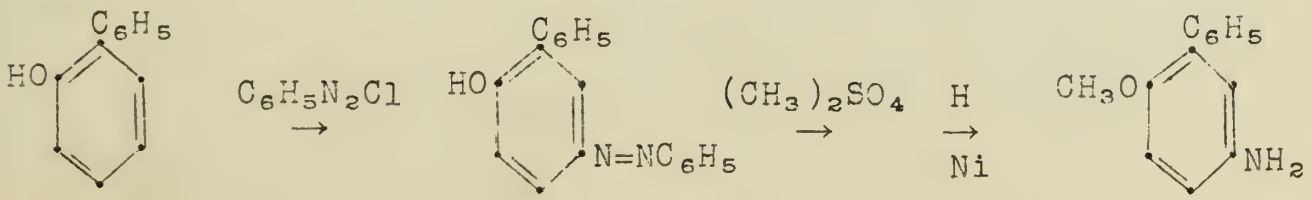
group was carried out by heating the amine with 3-diethylamino-propyl chloride. The final product proved to be inactive.

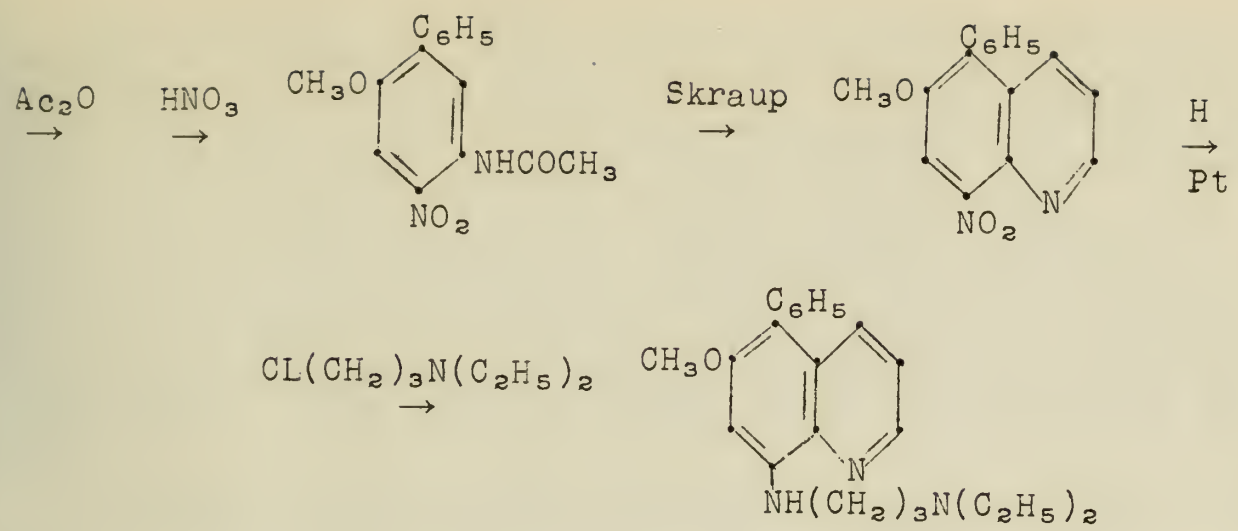
The effect of the substitution of the methylene group by a p-phenylene group was then determined.



The first step involved the preparation of the stabilized diazonium salt of 8-amino-6-methoxyquinoline using 1,5-naphthalene-disulfonic acid. Reaction of the stabilized salt with nitro-benzene gave a mixture of isomers from which 6-methoxy-8-p-nitro-phenylquinoline could be obtained by recrystallization; the structure of this compound was proved by acid permanganate oxida-tion to p-nitrobenzoic acid. The corresponding amine, obtained by a stannous chloride reduction, was alkylated with 3-diethyl-aminopropyl chloride. The introduction of the p-phenylene group rendered the compound practically inactive.

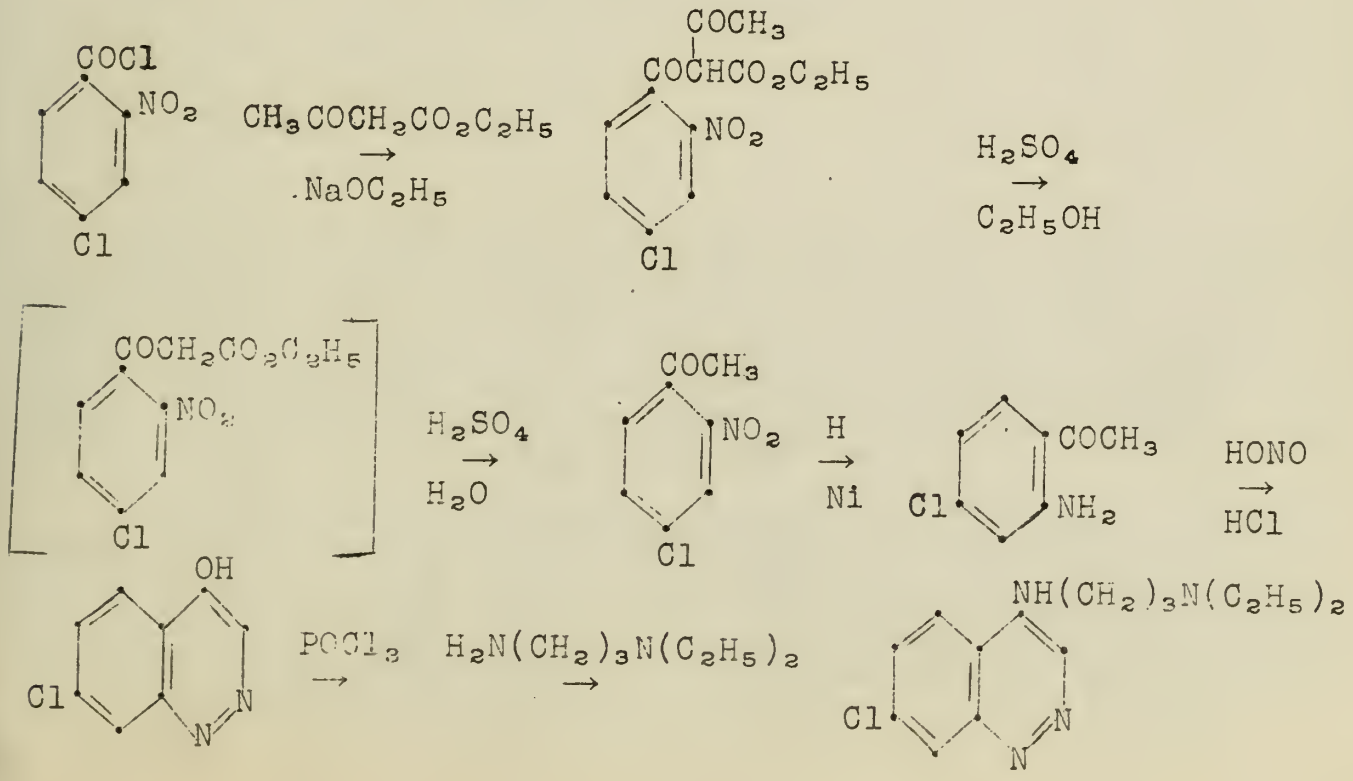
It was suggested that a possible reason for the high toxicity of plasmochin is an oxidative attack at position 5. It was de-cided to introduce a 5-phenyl group which might produce a blocking effect.





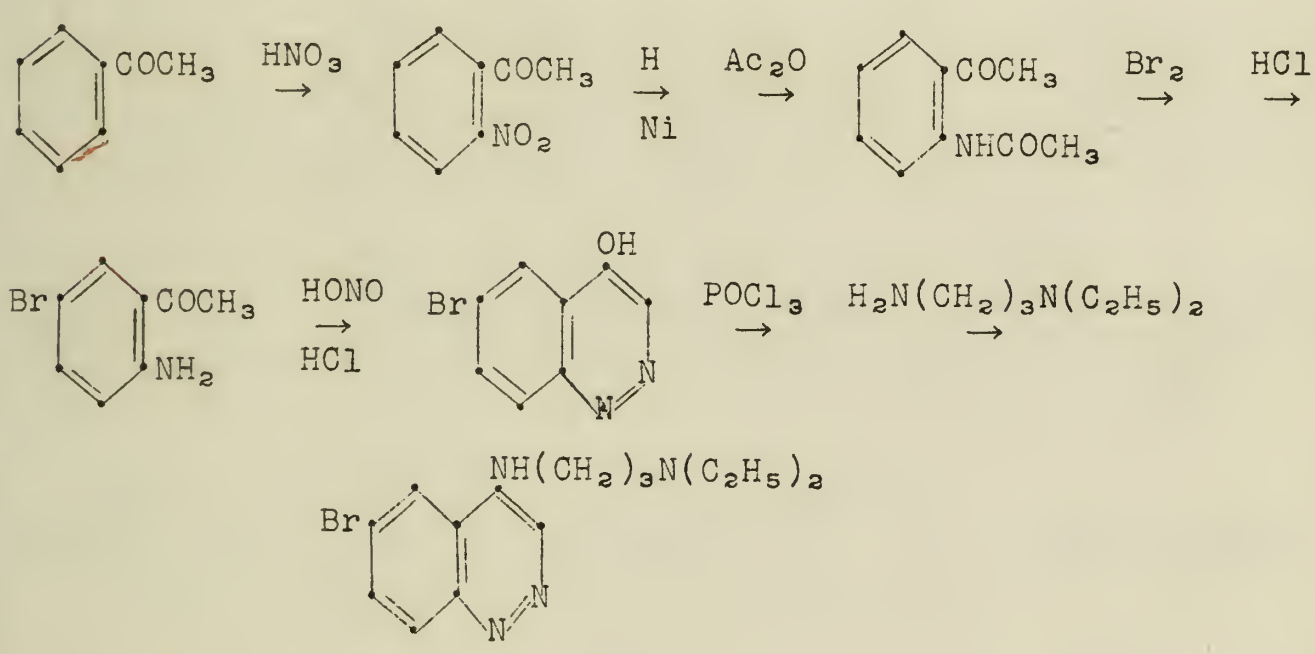
o-Phenylphenol was coupled with benzenediazonium chloride and the azo compound converted to the methyl ether which was catalytically reduced to the amine. After acetylation and nitration, a Skraup reaction gave 6-methoxy-8-nitro-5-phenylquinoline. This compound was reduced to the amine which was alkylated with diethylaminopropyl chloride. The desired drug showed no activity when tested.

In view of the structural similarities between the quinoline ring and the cinnoline ring, it was considered worthwhile to determine the antimalarial activity of the cinnoline analogs of some of the more promising quinolines.



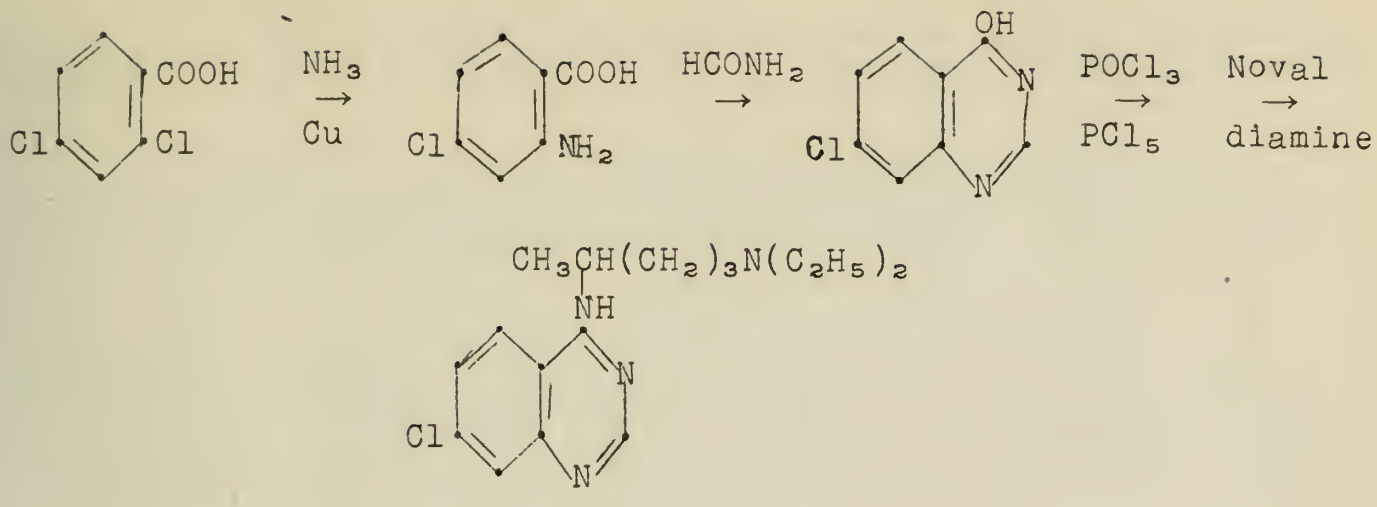
The synthesis of 7-chloro-4-(3-diethylaminopropylamino)-cinnoline involved the preparation of 2-amino-4-chloroacetophenone. This amine was prepared by the reduction of the corresponding nitro compound. 2-Nitro-4-chloroacetophenone was formed when 2-nitro-4-chlorobenzoyl chloride was allowed to condense with the sodium derivative of acetoacetic ester and the acetyl and carbethoxy groups removed from the condensation product by hydrolysis and decarboxylation. 2-Amino-4-chloroacetophenone was diazotized and the diazonium solution allowed to stand at 25° for ten days. This resulted in the formation of 7-chloro-4-hydroxycinnoline which was converted to the desired drug in the usual manner. This compound showed little promise as an anti-malarial.

6-Bromo-4-(3-diethylaminopropylamino)cinnoline was synthesized by the following method:



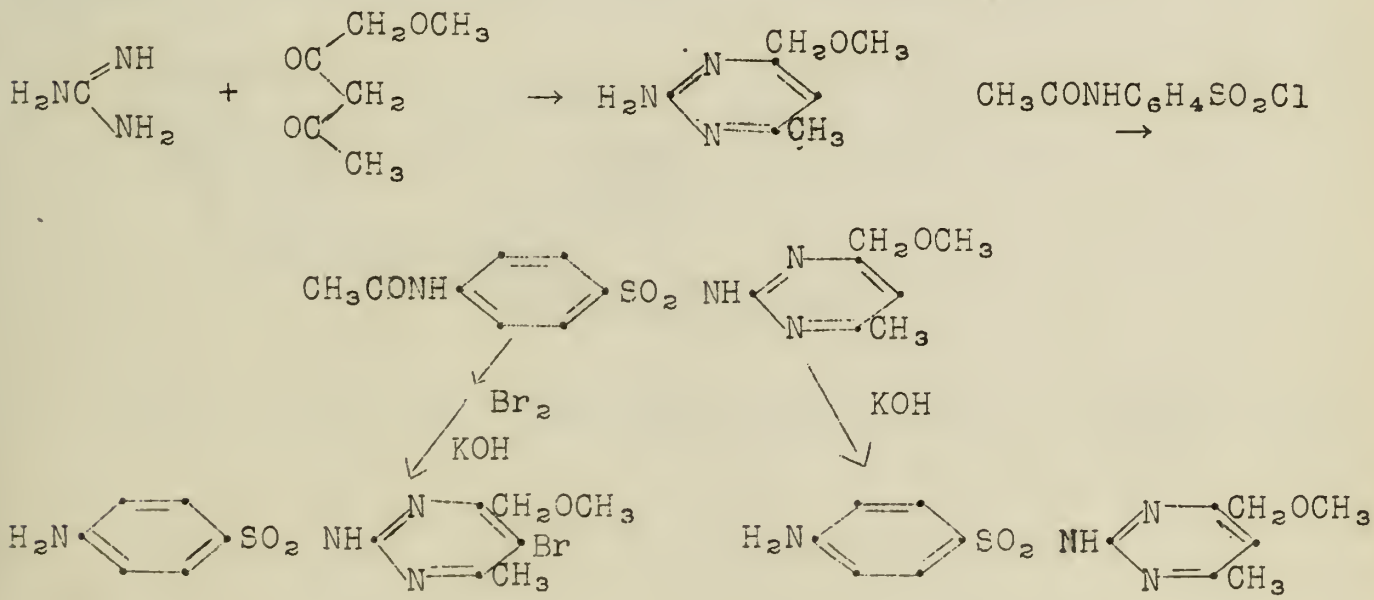
o-Nitroacetophenone, obtained, along with the m-isomer, by the nitration of acetophenone, was catalytically reduced to o-aminoacetophenone. This compound was first converted to the amide which upon bromination and subsequent hydrolysis gave 2-amino-5-bromoacetophenone. The synthesis was completed by a series of reactions similar to those previously described. The final product had a quinine equivalent of 0.5.

Certain quinazolines had previously been prepared, and although they were low in toxicity, they were also inactive as antimalarials. Since slight structural changes may greatly influence the activity, the further investigation of quinazolines was undertaken. As a result, 4-(4-diethylamino-1-methylbutylamino)-7-chloroquinazoline was prepared.



2,4-Dichlorobenzoic acid was converted to 4-chloroanthranilic acid in an autoclave by the action of ammonia in the presence of copper. The anthranilic acid reacted smoothly with formamide to give 4-hydroxy-7-chloroquinazoline which was converted in two steps to the quinazoline analog of 7618. This compound had a quinine equivalent of two against P. gallinaceum in chicks.

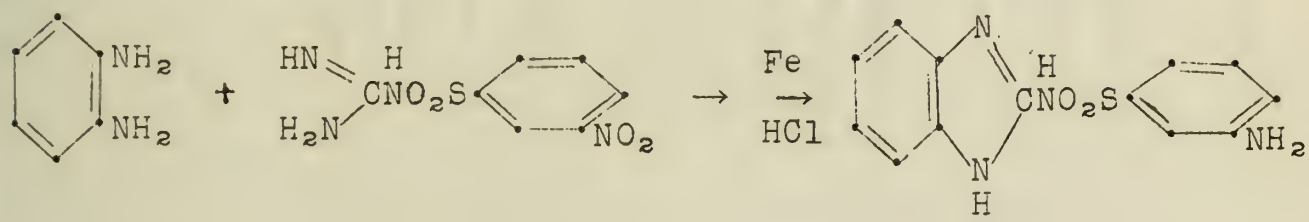
The sulfa drugs were being investigated mainly in the hope of finding a substance which would exhibit prophylactic action. Accordingly, the syntheses of 2-sulfanilamido-4-methyl-6-methoxymethylpyrimidine and its bromo derivative were undertaken.



Guanidine carbonate condensed with methoxyacetylacetone to give 2-amino-4-methyl-6-methoxymethylpyrimidine. This compound upon coupling with p-acetaminobenzesulfonyl chloride and subsequent hydrolysis of the acetyl group gave the desired sulfonamide. Bromination of the unhydrolyzed coupled product followed by

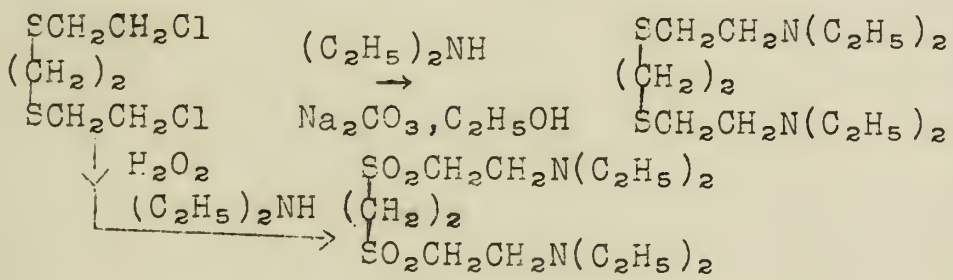
selective hydrolysis gave the bromine analog. These compounds showed very little activity either as suppressives or as preventives.

One phase of the investigation was concerned with the synthesis of compounds related to metanilamide. The synthesis of N^1-2-benzimidazolylmetanilamide was a result.



o-Phenylenediamine was condensed with m-nitrosulfaguanidine and then the nitro group of the condensation product was reduced with iron and hydrochloric acid. The final product possessed practically no activity.

Certain decamethylene diamines are known to exhibit antimalarial activity. Since the sulfur atom and the ethylene group are isosters, the diamino derivative of sesquimustard should be isosteric with an aliphatic ten carbon diamine. The bis(beta-diethylaminoethylthio)ethane was prepared from sesquimustard and diethyl amine. The corresponding disulfone was prepared in a similar manner from the disulfone of sesquimustard.



When tested, these compounds showed little or no activity.

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Reported by Gardner W. Stacy
and
Peter Kovacic
March 27, 1946

QUINAMINE

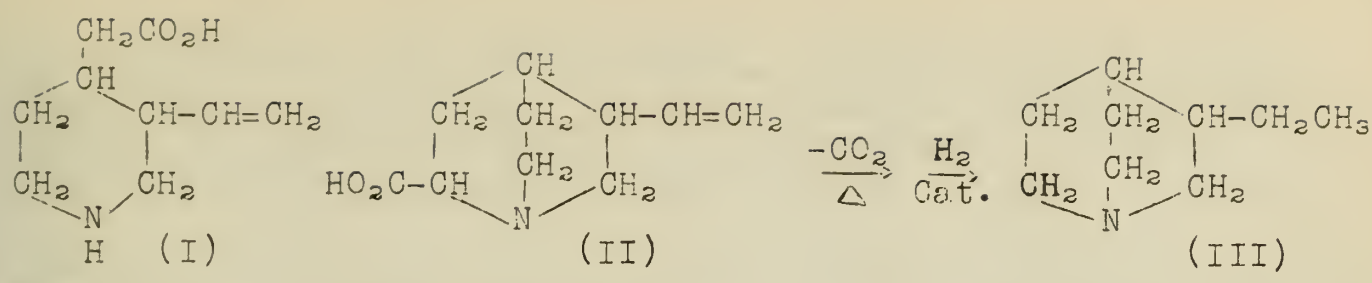
Quinamine, one of the minor alkaloids found in cinchona bark, was first isolated and characterized by Hesse in 1872. Investigation of quinamine was conducted during the period 1872-1881 by Hesse, deVrij, Howard, and Oudemans. Methods of extraction of the alkaloid from the bark were devised, and the formula was established after some controversy as $C_{19}H_{24}O_2N_2$. Hesse prepared several salts of the base, such as the gold and platinum chlorides, and quinamine was transformed into other substances, but nothing was done toward determining the structure of it.

Quinamine is obtained in about 0.1% yields, the amount varying somewhat with different barks, but since about ten other alkaloids are obtained in the same process, and Hesse was working with these others also, he didn't mind low yields. These same barks are the source of quinine so quantities of quinamine large enough for thorough investigation have been obtained in recent years as a by-product in the extraction of quinine.

Hesse found that quinamine on treatment with acetic anhydride at 60-80° yielded a substance he called acetylapoquinamine which was amorphous, but on hydrolysis it yielded a crystlline substance, $C_{19}H_{22}ON_2$, which he called apoquinamine and which differed from quinamine only by a molecule of water. He also obtained apoquinamine by treatment of quinamine with acids for short times at elevated temperatures. If smaller amounts of acids were used and ordinary temperatures, he also obtained two isomeric substances he called quinamidine and quinamicine and an amorphous residue. Hesse determined the formulas and properties of these substances, especially their specific rotations in about every known solvent, but nothing was done with structure determination.

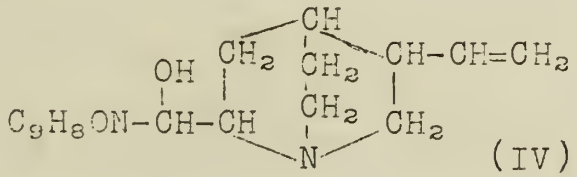
The natural cinchona alkaloids which are known may be represented by the general formula $Q-\underset{OH}{CH}-Q'$, where Q is quinoyl or 6-methoxyquinoyl and Q' is 3-vinyl- or 3-ethyl-quinuclidyl. Scission oxidations of these alkaloids produce cinchoninic acid or 6-methoxycinchoninic acid, and the quinuclidine nucleus suffers disruption into fragments, the largest of which is meroquinine (I). For example, quinine on chromic acid oxidation forms 6-methoxyquinoline-4-carboxylic acid. Quinamine aroused interest when Henry, Kirby, and Shaw in their investigations found that scission oxidation in no cases gave any derivative or probably fragment of quinoline.

Quinamine, on chromic acid oxidation, yields and acid, $C_{10}H_{15}O_2N$ (II), which contains an ethylenic linkage. On decarboxylation a base is formed, $C_9H_{15}N$, which on catalytic hydrogenation gives 3-ethylquinuclidine, $C_9H_{17}N$ (III), which was identified by comparison with some synthetic compound made for this purpose by Prelog's method. Assuming the attack is at the



Meroquinine 3-vinylquinuclidine-8-carboxylic acid 3-ethylquinuclidine

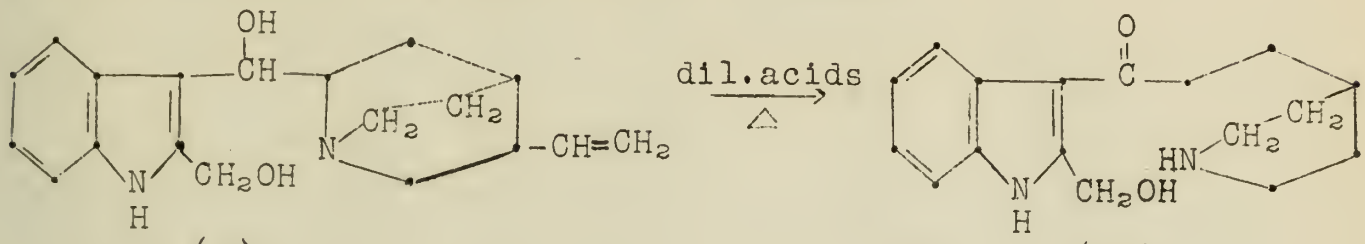
8 position via the central carbinol as in other cinchona alkaloids, the acid must be 3-vinylquinuclidine-8-carboxylic acid. Therefore the partial structure of quinamine can be written as structure (IV).



Although Zerewitinoff determinations indicated the presence of only two replaceable hydrogen atoms in quinamine, there is evidence that it contains three. When acetylapoquinamine forms, the central carbinol is acetylated, and the second hydroxyl is eliminated as water. A third replaceable hydrogen is present in the imino group of the C_9H_8ON nucleus since a nitrosoquinamine giving a Liebermann reaction has been prepared.

Nitric acid oxidation of quinamine gave picric acid and a compound, $C_9H_4O_7N_4$, which was not identified. A tetrahydroquinoline or an indole nucleus could have accounted for the picric acid (and be consistent with the formula for that part of the structure), and in consideration of the structures of other cinchona alkaloids the former seemed more probable. Attempts to dehydrogenate the compound proved unsuccessful. Quinamine with vanillin or piperonal in alcoholic HCl gives a rose color and with Ehrlich's reagent a purple color, both of which indicated an indole nucleus. The indole structure was finally proved when quinamine was heated with zinc dust at 320°, and 2,3-dimethylindole was isolated and identified by comparison with synthetic specimens made by Fischer's method. Since quinamine has 19 carbon atoms, and vinylquinuclidine-carboxylic acid and dimethylindole have 10 carbons apiece, one atom must form a connecting link, presumably that one which winds up in the carboxyl group. On phytochemical bases it must connect to the 3 position of the indole nucleus, so the complete structure of quinamine must be (V). Since quinamine is neither phenolic nor ketonic and forms a N-nitrosoquinamine, the two oxygen atoms must be present in carbinol groups, attached to the 2 and 3 positions of the indole nucleus. This structure is consistent with the other derivatives and their formations.

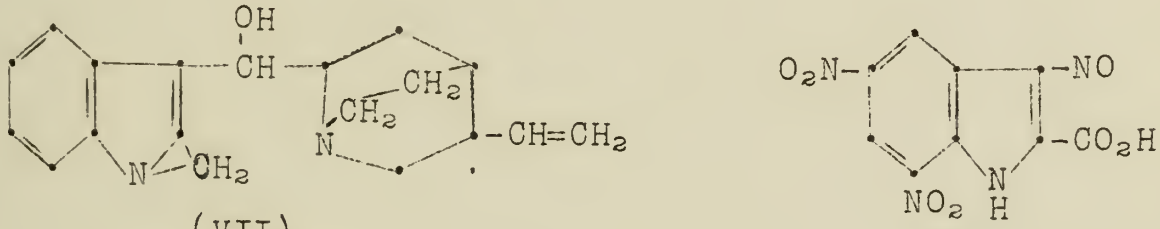
Quinamine, like other cinchona alkaloids, is converted on boiling with dilute acids into an isomeric quinacine, which Hesse called quinamicine. It is represented by formula (VI), and has been characterized by its derivatives: a picrate, a 2,4-dinitrophenylhydrazone, and an oxime.



(V)
Quinamine

(VI)
Quinamicine

The formation of apoquinamine on treatment with acids is due to the loss of water, and Kirby has proposed the structure (VII) for this compound. This structure is consistent with the fact that the N-nitrosoquinamine does not lose water on similar treatment. It has been hypothesized that the compound $C_9H_4O_7N_4$ which resulted when quinamine was oxidized with nitric acid is structure (VIII) from consideration of the structure of quinamine, although proof of this has not yet been accomplished.



(VII)
Apoquinamine

(VIII)

Catalytica hydrogenation of quinamine gives, by saturation of the vinyl side-chain of the quinuclidine, dihydroquinamine, which can be converted into a quinacine. Apoquinamine on catalytic hydrogenation yields dihydroapoquinamine and more slowly tetrahydroapoquinamine.

Quinoidine, an amorphous residue from the quinine manufacture containing several of the minor cinchona alkaloids, has been used as a cheap antimalarial drug. Quinamine itself has been found by Thron and Dirscherl to have no effect on avian malaria.

Indole alkaloids have been isolated from a number of botanically unrelated plants, but quinamine is the first recorded instance of such an alkaloid in Cinchona. It has been suggested by Robinson that the quinoline ring in quinine may have been formed in the plant from quinic acid; it seems likely, however, that the source of the indole nucleus in quinamine is tryptophane. If the 3-member ring proposed for apoquinamine exists and it were opened by rupture of the C-N bond in the pyrrole nucleus, a quinoline could result, which may be the connection between quinamine and the other known cinchona alkaloids.

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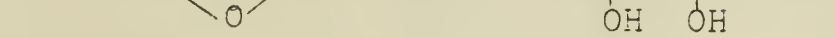
Reported by K. M. Beck
April 3, 1946

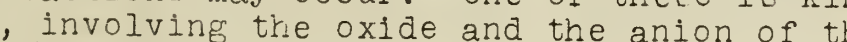
THE OPENING OF EPOXIDE RINGS

The opening of ethylene oxide in aqueous solution may occur in several different ways. There is first a slow uncatalyzed hydration to the glycol.



(I)

$v=k[S]$; where v is the velocity of the reaction and [S] the concentration of the ethylene oxide. In the presence of acids two further reactions may occur. One of these is kinetically second order, involving the oxide and the anion of the acid; thus with hydrochloric acid.



(II)

$v=k[S][Cl^-]$

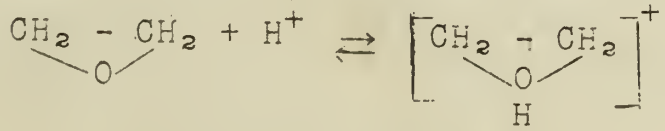
The other reaction leads to the same product but is kinetically third order.

(III) $v=k\,[S][Cl^-][H^+]$

The existence of reaction (II) can be shown by the rate of reaction of ethylene oxide with 0.1 m. potassium chloride. If reaction (II) did not occur, the rate of reaction of ethylene oxide with 0.1 m. of potassium chloride should be about one-millionth the rate of reaction of 0.1 m. hydrochloric acid, this being the ratio of the hydrogen ions. Actually the rate is about one-fiftieth as fast.

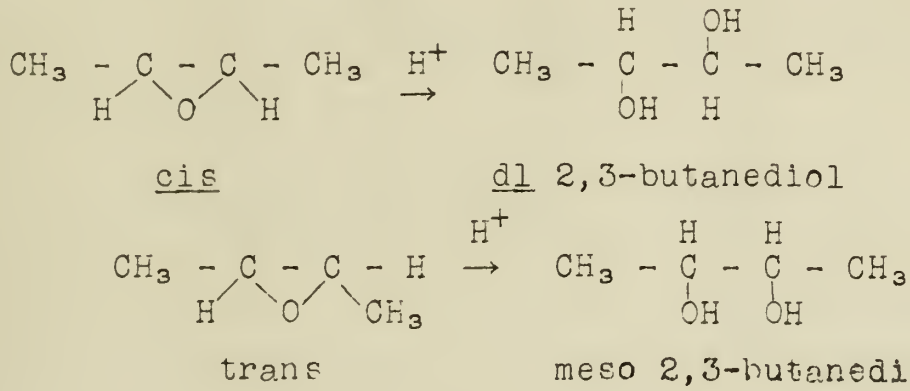
The mechanism of reaction (II) is a nucleophilic displacement on carbon. The displacing group is the halide ion and the displaced group, the bridge oxygen. However this remains attached to the molecule by virtue of the carbon-oxygen bond which is not involved in the displacement.

The acceleration of reaction (II) by acids is normal. The hydrogen proton adds to the oxygen in a reversible first step.



This produces an intermediate in which the carbon-oxygen linkage is greatly weakened allowing a more facile nucleophilic displacement.

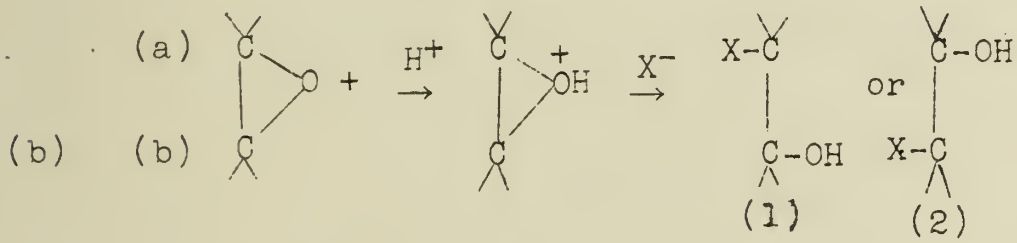
Since the attack of the negative group must take place at the rear of the molecule, the oxide ring being considered the front, inversion of configuration must necessarily take place. This has been demonstrated very effectively with the oxides of butene-2.



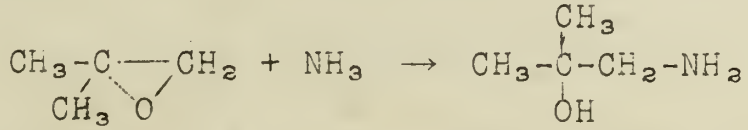
cis — dl 2,3-butanediol

trans — meso 2,3-butanediol

In symmetrically constituted epoxides, it was immaterial as to which carbon atom the nucleophilic reagent attacked. However, in unsymmetrical epoxides, two products can be formed depending upon which carbon atom is attacked. The following equations illustrate the attack of an unsymmetrical epoxide by a hydrogen halide.



If carbon (a) is attacked, product (1) is obtained while the attack of carbon (b) leads to product (2). A general rule which will predict the course of this type of reaction is given as follows. The nucleophilic reagent attacks the least substituted carbon atom, therefore that carbon atom of the lowest electron density. This will lead to alcohols with the greatest degree of branching at the carbinol-carbon atom. This type of reaction has been observed with a large variety of reagents such as halides, phenoxides, ammonia, amines, mercaptans, etc.

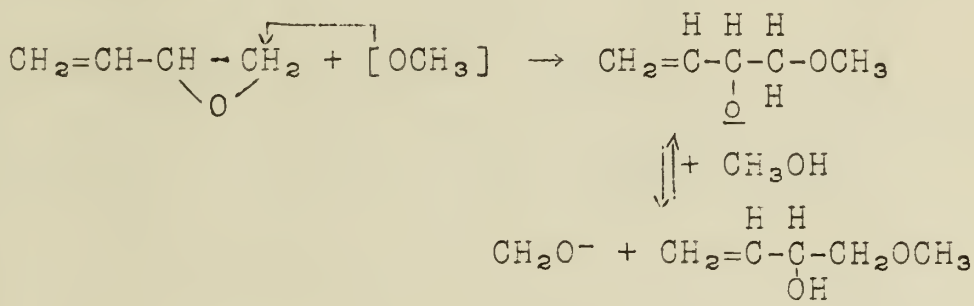


isobutylene oxide — aminotrimethylcarbinol

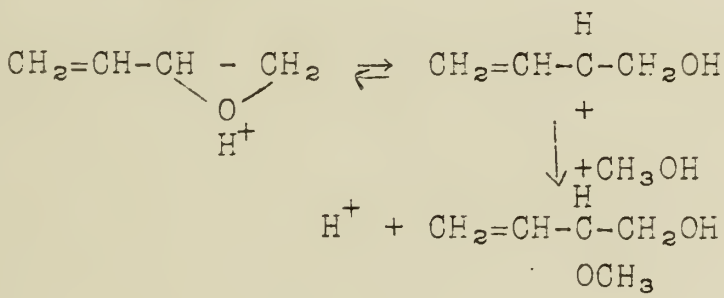
There are a few notable exceptions to the above normal mode of addition. One of these is 3,4-epoxy-1-butene which reacts

abnormally with methanol in acidic solution to give 2-methoxy-3-buten-1-ol and normally with methanol in the presence of a little sodium to give 1-methoxy-3-buten-2-ol.

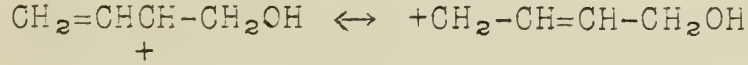
The following mechanism may be advanced to explain the two different types of addition. The normal reaction which occurs with methanol, in the presence of a little sodium, is due to a bimolecular nucleophilic displacement by the methoxide ion which is then regenerated.



This type of S_N^2 mechanism might be expected to lead to the normal product in the acid-catalyzed reaction. If, instead, a unimolecular ring opening occurs, the formation of the abnormal product would be expected.



The unimolecular ring opening is assisted by the resonance stabilization of the intermediate carbonium ion.



As further proof of these resonance hybrids, there was obtained from the addition of hydrochloric acid to the above epoxide a small higher boiling fraction which was identified as 1-chloro-2-buten-4-ol. This would correspond to addition of the chloride ion to the second resonance form.

Other examples of substances which react abnormally under acidic influence are 2-chloro-3,4-epoxy-1-butene, 1-bromo-3,4-epoxy-1-butene and styrene oxide. In contradiction to this

theory of acid-catalyzed abnormal addition is the report that styrene oxide reacts with alcohols in the presence of sulfuric or phosphoric acid to give normal addition. However, no proof of the structure was given in this instance.

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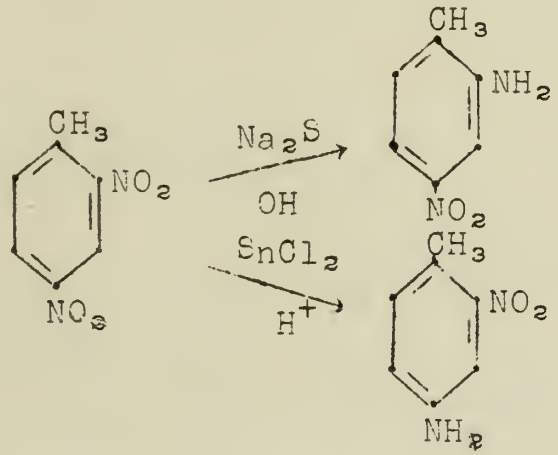
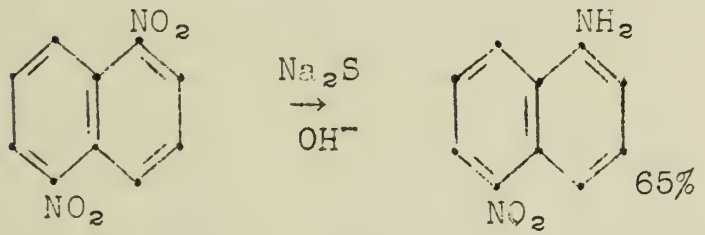
Reported by S. L. Meisel
April 3, 1946

THE SELECTIVE REDUCTION OF NITRO GROUPS
IN AROMATIC POLYNITRO COMPOUNDS

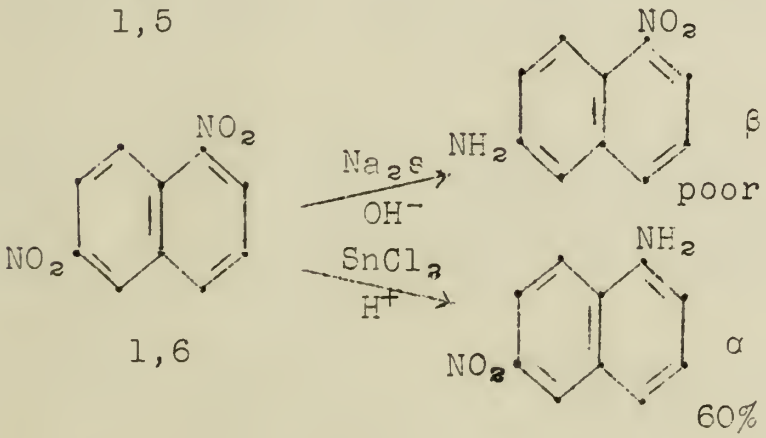
The familiar reduction of m-dinitro benzene to m-nitro aniline by such agents as Na_2S in alkaline medium, of $SnCl_2$ in acid media, does not necessarily constitute a selective reduction. However, in the case of 2,4-dinitrotoluene, the alkaline sulfide reagent produces 4-nitro-2-amino toluene whereas the acid stannous chloride produces the 2-nitro, 4-amino toluene. (1)



This effect is also apparent among the dinitronaphthalenes.

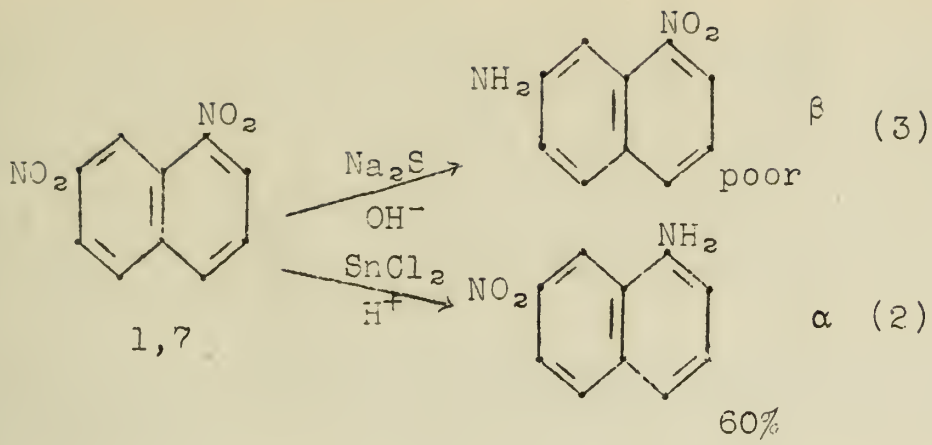


(2)

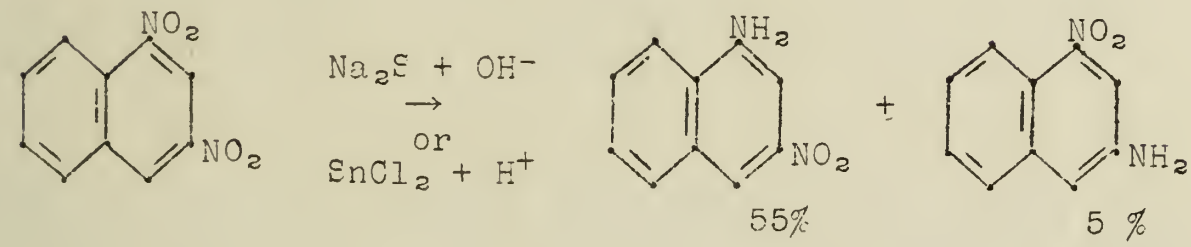


β (3)

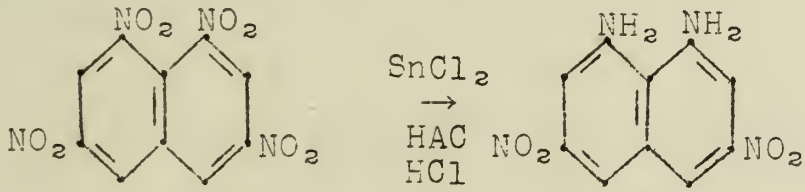
α (2)



However, no distinction is made by either reagent in the case of 1,3-dinitronaphthalene (2)



Hodgson (4) extended the use of the $SnCl_2$-HAC-HCl solution to reduce selectively 1,3,6,8-tetra-nitronaphthalene, unsuccessfully attempted by Wills with alkaline Na_2S

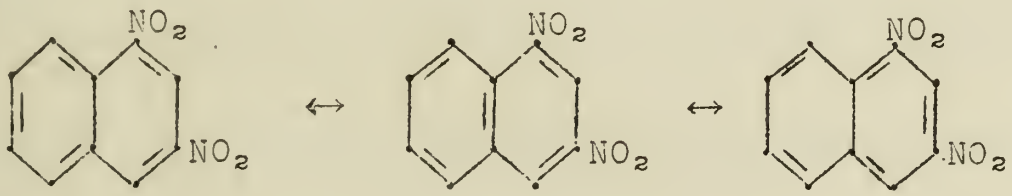


The preferential reduction of the α-positions further substantiates the selectivity of this reagent. The constitution of the diamine was established by diazotization and conversion to dichloro and dibromo derivatives, deamination to 2,7-dinitronaphthalene, and reaction with acetone to give the 5,8-dinitrodimethyl-dihydro perimidine.

It appears, then, that in the naphthalene series, acid reducing agents attack the α-position preferentially, whereas alkaline sulfide reagents selectively reduce the β-position when the α, β groups are in different nuclei.

Hodgson and Elliot (5) explain this difference in positional reactivity as being due to the negative inductive effect of the second nucleus, since by it the α-nitro groups will be more electropositive than the β-group, and being at the end of a conjugate chain in two of the three structures held for naphthalene, it will be more susceptible to attack by atomic hydrogen in the acid medium. Once a nitro group is reduced, the electronic strain due to it will be relieved, rendering the second groups less susceptible to attack.

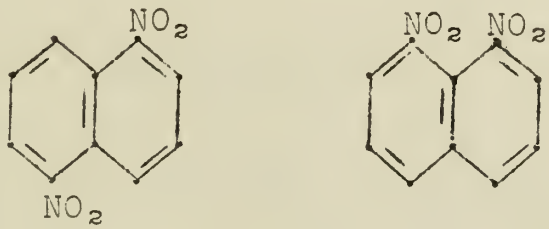
When the nitro groups are homonuclear as in 1,3-dinitronaphthalene, the α- is mainly attacked, but due to the resonance forms possible



a b c

Some c is present in which the β-nitro is now at the end of the conjugate chain, and also relieved of the inductive effect of the second nucleus by the absence of the restricting double bond, and consequently more susceptible to attack. This resonance will account for the small amount of 1-nitro-3-napthylamine formed by both reagents.

When both groups are in α-position as in 1,5 and 1,8 dinitronaphthalenes,



(2)

1,5 1,8

the groups are identical in situation and are attacked simultaneously by the acid reducing agent to form the respective diamines.

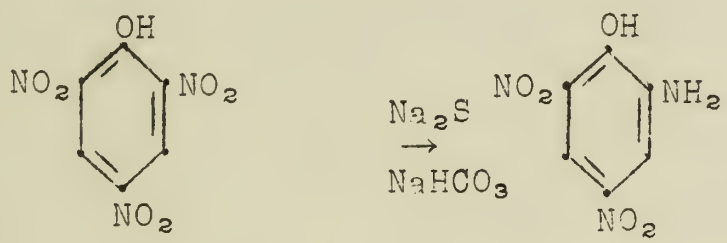
The alkaline sulfide reduction apparently takes place by an oxidation of the sulfur by the nitro group rather than a reduction of the nitro group. Therefore, the ease of detachment of the

oxygen atoms will determine which group is reduced. Since the α group has been shown to be the more electro positive, the β group in heteronuclear dinitro compounds will function as the oxidizing agent.

The poorer yields from alkaline reductions are attributed to the poorer reducing potential of alkaline sulfide solutions, so that incomplete reduction takes place.

Application to benzene derivatives.--By the same considerations as applied to α-β-dinitronaphthalenes, it follows that in 2,4-dinitrotoluene, the 4-nitro will be more electropositive since it is farther from the positive inductive effect of the methyl group, so it will be preferentially reduced by acid agents (negative). In a similar manner the 2-nitro will be less positive and its oxygen atoms will be more available for oxidation of the sulfide reagents.

Hodgson has extended this concept to produce a quantitative reduction of picric acid to picramic acid (6).



Apparently the first reduction is sufficient to decrease the oxidizing potential of the remaining β-nitro group below that required for further reaction with the alkaline sulfide.

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Reported by Robert L. Myers
April 10, 1946

THE HYDROGEN BOND: ITS RELATION TO TAUTOMERISM AND MOLECULAR ASSOCIATION

Louis Hunter, University College, Leicester

The idea that hydrogen can hold two other atoms together was conceived by Oddo (1906), Moore and Winmill (1912), and Pfeiffer (1913). Since that time many workers have conducted investigations to discover the scope and limitations of this concept. The important part played by the hydrogen bond in determining the solubility, volatility, crystal structure, and heats of solution and mixing of certain compounds is well known.

During the past few years Hunter has considered the hydrogen bond in relation to two other phenomena, tautomerism and molecular association. On the basis of experimental data, he has been able to classify tautomeric substances into two groups, depending on whether or not the hydrogen bond is involved.

I. <u>Compounds exhibiting classical tautomerism (prototropy)</u>.--Tautomerism has long been considered an ionic process and, as the name "prototropy" suggests, it involves the migration of a proton from one spot in the molecule to another, with an accompanying shift of electrons along the rest of the chain. Hunter does not discredit such a mechanism, since it has ample experimental verification - instead, he includes the compounds which exhibit this behavior in one group of tautomeric compounds, among which is the familiar keto-enol system.

1. Keto-enol	$-CH_2C(=O)-$	$\rightleftarrows$	$-CH=C(OH)-$
2. Allylic	$-CH=CHCH_2-$	$\rightleftarrows$	$-CH_2CH=CH-$
3. Azomethine	$-CH=NCH_2-$	$\rightleftarrows$	$-CH_2N=CH-$
4. Nitro-<u>aci</u>-nitro	$-CH_2NO_2$	$\rightleftarrows$	$-CH=N(OH)(\rightarrow O)$

It should be noted that, in all the systems listed above, at least one of the alternate points of attachment of the proton is a carbon atom. The significance of this will be mentioned later.

II. <u>Compounds exhibiting mesohydric tautomerism</u>.--Hunter's early papers presented proof that molecular association was a result of hydrogen bonding and that replacement of the bonding hydrogen atoms removed the tendency toward association. The boiling point, solubility, wet melting point, and apparent molecular weight were the criteria used to determine the extent of association.

In 1941 Hunter observed that many types of compounds which exhibited molecular association simultaneously showed tautomeric behavior. The amides, for example, have the abnormal physical properties of associated compounds; moreover, they are capable of yielding N-substituted and O-substituted derivatives under the proper conditions. It was suggested that, in such compounds, the tautomeric behavior and molecular association were due to the same cause - the intermolecular sharing of the hydrogen atom responsible for tautomeric behavior. At no time would it be necessary for the hydrogen ion to appear as a separate entity. If this suggestion is true, then it follows that there is a fundamental distinction between the type of tautomerism exhibited in compounds of group I and that under discussion at present.

In general, a tautomeric compound may be represented as $\underbrace{A\text{———}B}_{H}$ where A and B may be united or where they may be separated by a chain of atoms. Thus, classical tautomerism may be represented by the following equation, where at least one of the atoms A and B must be carbon, HA———B ⇄ A———BH. If neither A nor B is carbon, but rather such an atom as oxygen, nitrogen, or sulfur, then the above compound exhibits hydrogen bond association. Since hydrogen bonding has its origin in resonance, two electronic configurations must be conceivable; the actual compound will be a resonance hybrid of such structures and will be homogeneous.

$$\cdots HA\text{———}B\cdots HA\text{———}B\cdots HA\text{———}B\cdots \qquad (a)$$

$$\leftrightarrow \quad \text{——}H\cdots A\text{———}BH\cdots A\text{———}BH\cdots A\text{———}B\text{——} \qquad (b)$$

I

The associated molecule may be either a straight chain as indicated, or it may exist as a cyclic dimer as in oximes, carboxylic acids, and pyrazoles. The tautomeric behavior of the compound with resonance forms (a) and (b) is a result of the fact that its chemical properties are intermediate between (a) and (b). When I enters into chemical reaction, its dissociation can follow either of two routes, yielding either HA———B or A———BH as a transitory product according to the nature of the other components of the reaction mixture. Since the hydrogen atom in the associated molecule occupies a position between the two reactive centers, rather than being attached specifically to any one atom, this type of tautomerism has been termed <u>mesohydric tautomerism</u>. It is a form of resonance. In order to apply equation I to a specific case, the amides again will be mentioned.

$$\cdots \underset{R'}{\overset{R}{HN\text{-}C}}{=}O\cdots \underset{R'}{\overset{R}{HN\text{-}C}}{=}O\cdots \underset{R'}{\overset{R}{HN\text{-}C}}{=}O\cdots \quad \leftrightarrow \quad \text{—}H\cdots \underset{R'}{\overset{R}{N{=}C}}\text{-}OH\cdots \underset{R'}{\overset{R}{N{=}C}}\text{-}OH\cdots \underset{R'}{\overset{R}{N{=}C}}\text{-}O\text{—}$$

The following tautomeric systems previously have been regarded as showing prototropy, but now are attributed to mesohydric tautomerism. They are classified according to the number of atoms separating successive hydrogen bonds.

Dyad systems

Pyrazoles =NNH- Oximes =NOH

Triad systems

Amides	-CONH-	Sulfonamides	$-SO_2NH-$
Hydrazides	-CONHNH-	Benztriazoles	-N=NNH-
Amidines	-N=CHNH-(cyclic)	Diazoamino compounds	-N=N-NH-
Cyanamides	-NHCN	Carboxylic acids	-COOH
Thioamides	-CSNH-		

Tetrad systems

Hydroxytriazenes $-N=NN(OH)-$

Pentad systems

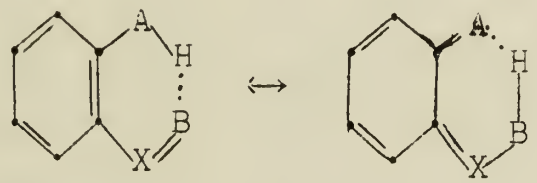
o-Hydroxyazo compounds
Arylazo-oximes
Formazyl compounds
Thioacridone
Enolized β-diketones and β-keto-esters
Phenols and arylacylamide compounds with donor groups in the o-position.

The fundamental differences between classical tautomerism and mesohydric tautomerism may be summarized.

Classical Tautomerism. (1) In classical tautomerism the members of a tautomeric pair have a separate existence. Separation can be effected if the techniques available are more rapid than the rate of interchange of the tautomers. (2) Since at least one of the alternate points of attachment of the tautomeric hydrogen is a carbon atom, no hydrogen bonds of the type A-H-B can be formed.

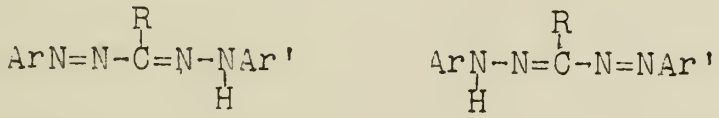
Mesohydric tautomerism. (1) Although the tautomeric system has dual character, it is essentially homogeneous, and attempts to isolate tautomers will prove futile. There are several reports in the literature of the isolation of tautomers of compounds which fall in Group II - Hunter has shown that the alleged isomerism can be explained by the presence of impurities or by some other

means. (2) Hydrogen bonding is an essential part of mesohydric tautomerism. The hydrogen bonds usually produce long associated molecules or cyclic dimers. Although mesohydric tautomerism was first manifest in connection with such associated molecules, it was later realized that five- and six-membered chelate ring systems involving hydrogen provide a special case of the mesohydric structure in which the tautomeric hydrogen is shared between A and B in the same molecule. Examples of this type of

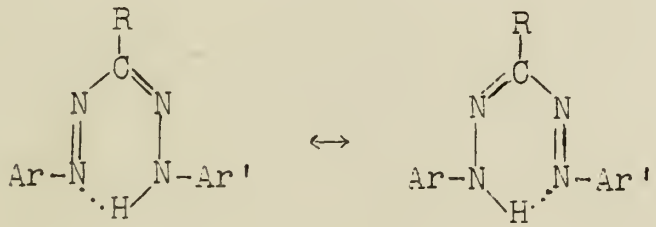


mesohydric tautomerism are numerous, and several are listed above under "tetrad and pentad systems."

Finally, an example of the use of the theory of mesohydric tautomerism is given. There have been several reports of the isolation of isomeric formazyls. This is a pentad system in which



A and B are nitrogen. No tautomeric forms should be separable - instead, hydrogen bonding should give rise to two resonating forms probably cyclic. Hunter showed that one of the alleged



isomers was an impure form of the other.

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Reported by Edgar Howard, Jr.
April 10, 1946

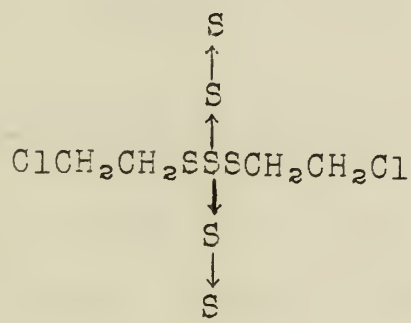
THE LEVINSTEIN PROCESS FOR MUSTARD GAS

The production of mustard gas was developed on an industrial scale by the firm of Levinstein, Ltd., during World War I. The Levinstein process was based on the original procedure of Guthrie which was discovered in 1860 and which consisted in the condensation of ethylene with sulfur monochloride.

$$2\ CH_2{=}CH_2 + S_2Cl_2 \rightarrow ClCH_2CH_2SCH_2CH_2Cl + [S]$$

At the outbreak of World War II an intensive study of Levinstein mustard gas was undertaken by the Americans. A part of this program was to study the Levinstein process with particular reference to the composition, properties and mode of formation of the impurities. It is proposed here to report some of the results of this investigation.

When Levinstein mustard gas is subjected to prolonged treatment with water an unhydrolyzed residue is obtained which corresponds to about 30% of the original charge and consists of <u>bis</u>-2-chloroethyl polysulfides $[(ClCH_2CH_2)_2S_x]$, varying in average composition from that of the hexa- to that of the nonasulfide. Treatment with cellosolve causes the separation of sulfur and yields nearly pure pentasulfide. The pentasulfide can be stripped by treatment with ammonia in a solvent such as ether to yield <u>bis</u>-2-chloroethyl trisulfide. The polysulfides are believed to be derived from the trisulfide by coordination of sulfur with the central sulfur atom in the trisulfide. The heptasulfide, for example, is thought to have the following structure.



Chlorination converts <u>bis</u>-2-chloroethyl disulfide to 2-chloroethylsulfenyl chloride, which is believed to be an intermediate in the formation of mustard gas from ethylene and sulfur chlorides. Condensation of the sulfenyl chloride with

$$ClCH_2CH_2S\text{-}SCH_2CH_2Cl + Cl_2 \rightarrow 2\ ClCH_2CH_2SCl$$

olefins produces mustard gas or its analogs. When propylene is used the product is 2-chloroethyl 2-chloro-n-propyl sulfide. It has been shown that the corresponding isopropyl derivative rearranges spontaneously to the normal isomer.

$$ClCH_2CH_2SCl + CH_2{=}CH_2 \rightarrow ClCH_2CH_2SCH_2CH_2Cl$$

$$ClCH_2CH_2SCl + HC{\equiv}CH \rightarrow ClCH_2CH_2SCH{=}CHCl$$

$$ClCH_2CH_2SCl + CH_3CH{=}CH_2 \rightarrow ClCH_2CH_2SCH_2\underset{\underset{Cl}{|}}{C}HCH_3$$

A mechanism has been proposed which accounts satisfactorily for the composition of Levinstein mustard gas. Such a mechanism must explain not only the formation of the polysulfides derived from the linear trisulfide but account also for the virtual absence of the disulfide and of free sulfur.

Sulfur monochloride may react as such with ethylene to produce bis-2-chloroethyl disulfide. The virtual absence of the

$$ClSSCl + 2CH_2{=}CH_2 \rightarrow ClCH_2CH_2SSCH_2CH_2Cl$$

disulfide in Levinstein mustard may be ascribed to the fact that sulfur monochloride converts it rapidly to the sulfenyl chloride. Ethylene could react with the sulfenyl chloride and

$$ClCH_2CH_2SSCH_2CH_2Cl + 3S_2Cl_2 \rightarrow 2ClCH_2CH_2SCl + 2S_3Cl_2$$

sulfur tritadichloride formed to produce, respectively, mustard gas and bis-2-chloroethyl trisulfide. The polysulfides are

$$ClCH_2CH_2SCl + CH_2{=}CH_2 \rightarrow ClCH_2CH_2SCH_2CH_2Cl$$

$$S_3Cl_2 + CH_2{=}CH_2 \rightarrow ClCH_2CH_2SSSCH_2CH_2Cl$$

produced by the sulfurization of the trisulfide by sulfur monochloride. The reaction of sulfur dichloride with ethylene is

$$ClCH_2CH_2SSSCH_2CH_2Cl + S_2Cl_2 \rightarrow (ClCH_2CH_2)_2S_x + SCl_2$$

known to be rapid.

$$SCl_2 + CH_2{=}CH_2 \rightarrow ClCH_2CH_2SCl \xrightarrow{C_2H_4} \text{mustard gas}$$

The net result of this series of reactions is the production of a mixture of bis(2-chloroethyl)sulfide and the corresponding polysulfides.

There is chemical as well as physical evidence to support the assumption that sulfur monochloride may undergo disproportionation to form sulfur dichloride and sulfur tritadichloride. If

$$2S_2Cl_2 \rightleftarrows SCl_2 + S_3Cl_2$$

this occurred in the Levinstein process, then each of these forms could react with ethylene as represented in the above series of equations.

Bibliography

The material reported in this seminar was taken from a series of papers by Fuson and co-workers to appear in the Journal of Organic Chemistry.

Reported by William E. Parham
and
Lester J. Reed
April 17, 1946

THE FORMATION AND STRUCTURE OF GR-S AND RELATED POLYMERS[1]

The name GR-S (Government Rubber-Styrene type) is an entity in itself and represents specifically a soluble copolymer of butadiene and styrene prepared in an emulsion with the use of a modifier. As this type of copolymer represents the bulk of the synthetic rubber produced during the past war, some cursory observations of its formation and structure are pertinent. Since it is impossible in a seminar of this length to explain even briefly the subtle innuendos of an emulsion polymerization system, only a few of the more organic aspects will be considered.

The essential constituents of the GR-S system are the monomers, butadiene and styrene, a water-soluble peroxide such as potassium persulfate, water, and emulsifier such as a fatty-acid soap and a modifier.

I. The Role of the Emulsifier

A. The Loci of the Reaction:

Harkins[2] and coworkers have presented excellent evidence to indicate that 1) the polymerization is initiated in the soap micelles, 2) as the soap disappears from its micelles, the locus of the reaction shifts to the polymer-monomer particles.

II. Initiation and Promotor Activity[3]

There is evidence to indicate that lauryl mercaptan functions as a promotor by virtue of the ability of the mercaptide ion to be oxidized by persulfate to provide a source of free radicals. Other mechanisms, however, may play a prominent role in the initiation step. The role of oxygen in the initiation step is, as yet, not clearly defined.

III. Modifier Action

The modifier acts as a chain transfer agent. Thus lauryl mercaptan[4,5] may react with a polymer molecule to stop its growth but producing a new radical which may start a new polymer chain. Thus, the modifier regulates the molecular weight of the copolymer and prevents excessive branching and cross-linking.

IV. The Structure of a GR-S Polymer

A. The Degradation of GR-S by Ozonolysis

One of the factors determining the intramolecular homogeneity of butadiene-type synthetic rubber is the extent to which

the diene enters the polymer by 1,4-addition versus 1,2-addition. A second factor involves the arrangement of the two or more monomers throughout the polymer chain.

1) Total Structure Determination: This approach is not new. Harries[6] was the first to describe the method; Pummerer, Ebermoger and Gerlach[7] and Pummerer and Richtzenbain[8] have applied it to natural rubber; Alekseeva and Belitskaya[9] to a 1:1 butadiene styrene copolymer; Hill, Lewis and Simonsen[10] to polybutadiene and to a butadiene-methyl methacrylate copolymer; Alekseeva[11] to a copolymer of butadiene and a mixed polymer of butadiene and methacrylonitrile, and Klebanskii and Vasileva[12] to polychloroprene.

Figure 1 illustrates the fragments which might be expected from an oxidative ozonolysis of a portion of the GR-S molecule.

FIGURE I

The following results have been determined on two samples of GR-S, one standard sample (G-1) (0.390 modifier), and one insoluble, G-23 (undermodified 0.15 per cent modifier)[13].

In Table I are shown the quantities of formic acid obtained from 100 g. of each of the samples studied, together with the percentages of butadiene accounted for in this manner. The values do not indicate any significant difference between samples G-1 and G-23.

TABLE I

Volatile Acids from Ozonization

	G-1	G-23
Formic Acid per 100 g. of rubber	19.5 g.	16.8 g.
Butadiene equivalent	23.0 g.	19.8 g.
Percentage of butadiene accounted for assuming the rubber is 77% butadiene	29.9	25.7

Table II shows the amount of succinic acid and identified esters from water soluble acids obtained from 100 g. of each of the samples, G-1 and G-23, together with amounts of butadiene and styrene accounted for.

TABLE II

FIGURE I

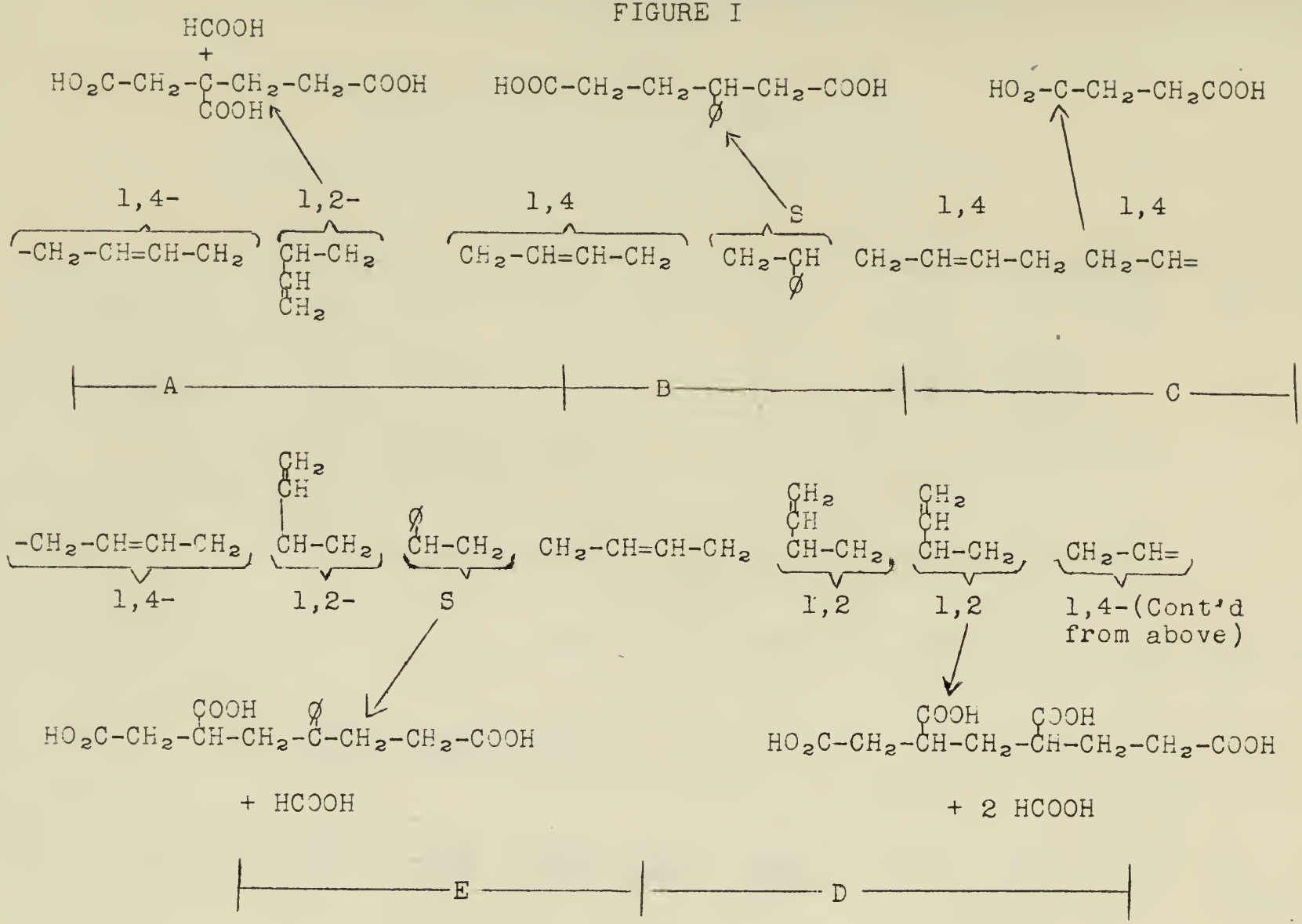

HCOOH
+
HO2C-CH2-C-CH2-CH2-COOH
COOH
HOOC-CH2-CH2-CH-CH2-COOH
Ø
HO2-C-CH2-CH2COOH
1,4-
1,2-
1,4
S
1,4
1,4
-CH2-CH=CH-CH2
CH-CH2
CH
CH2
CH2-CH=CH-CH2
CH2-CH
Ø
CH2-CH=CH-CH2
CH2-CH=
A
B
C
CH2
CH
-CH2-CH=CH-CH2
CH-CH2
Ø
CH-CH2
CH2-CH=CH-CH2
CH2
CH
CH-CH2
CH2
CH
CH-CH2
CH2-CH=
1,4-
1,2-
S
1,2
1,2
1,4-(Cont'd from above)
COOH
Ø
HO2C-CH2-CH-CH2-C-CH2-CH2-COOH
+ HCOOH
COOH
COOH
HO2C-CH2-CH-CH2-CH-CH2-CH2-COOH
+ 2 HCOOH
E
D

TABLE II

Compounds from Water-soluble Acids

(Based on 100 grams of Extracted Rubber Samples)

Compounds Isolated	G-1					G-23				
		Butadiene		Styrene			Butadiene		Styrene	
	Wt.g.	g.	%	g.	%	Wt.g.	g.	%	g.	%
1) Succinic Acid	37.05	16.93				30.64	14.02			
2) Dimethyl Succinate	37.81	14.00				37.85	14.00			
Total acid and ester		30.93	40.2				28.02	36.4		
3) Trimethylbutane-1,2,4-tricarboxylate	28.62	13.32	17.3			25.32	11.80	15.3		
4) Dimethyl-β-phenyladipate	11.44	2.47	3.2	4.76	20.7	8.80	1.90	2.5	3.66	15.9
5) Tetramethylhexane-1,x,y,6-tetracarboxylate	6.44	3.28	4.3			6.92	3.53	4.6		
6) Trimethyl x-phenylhexane-1,y,6-tricarboxylate	4.86	1.56	2.0	1.50	6.5	5.17	1.66	2.2	1.60	7.0
		51.56	67.0	6.26	27.2		46.91	61.0	5.26	22.9

From reference to Figure I, it can be seen that in order for the polymer chain to be cleaved by ozone, there must be present a butadiene molecule which has entered by 1,4-addition. Thus, the general formula for the esters derived from the cleavage products of a butadiene-styrene copolymer is

$$RO\text{-}COCH_2\text{-}\left[\begin{array}{c} CH_2\text{-}CH \\ | \\ COOR \end{array}\right]_m - \left[\begin{array}{c} -CH_2\text{-}CH \\ | \\ \emptyset \end{array}\right]_n -CH_2COOR$$

without regard to arrangement of internal units. Then tetramethylene hexane-1,x,y,6-tetracarboxylate would be represented by the above formula, where m = 2 and n = 0 and trimethyl-x-phenylhexane-1,y,6-tricarboxylate would be represented by the same formula where m = 1, n = 1.

The water-insoluble acids were converted to their methyl esters but they could not be fractionated or otherwise separated for characterization. Analysis and refractive index measurements of some unidentified distillates, coupled with the knowledge of the identity of certain esters isolated by earlier workers, led to the tentative identification of these small portions as octane pentacarboxylic ester (m = 3, n = 0), phenyloctane tetracarboxylic ester (m = 0, n = 2) and fumaric ester.

2) Determination of Terminal Vinyl Groups

a) Influence of Temperature on 1,4- and 1,2-Addition:

The results show that changes in temperature of polymerization are without effect upon the mode of butadiene addition.

This is in marked contrast to polybutadienes prepared under different conditions. Ziegler, Grimm and Willer[14] have concluded from analyses based on ozonolysis and on the separation of the paraffins obtained by the reduction of polybutadienes prepared under various conditions (see below) that the polymerization temperature is the most important factor which influences the nature of butadiene addition. It was shown that in the case of low polymers made with lithium butyl or potassium phenylisopropyl at temperatures from -50 to 100° the amount of 1,4-addition increased from 5 to 80 per cent. Recently Yakubchik, Vasilev and Zhabina[15] have reported the vinyl content of several polybutadienes and copolymers by means of the ozonolysis procedure. They have found that an increase in temperature leads to a higher percentage of 1,4-polymerization in the case of sodium polybutadienes. In general, they found that emulsion copolymers of butadiene and styrene possess a lower vinyl content than sodium polymerized polybutadiene.

b) Influence of Other Variables on 1,4- and 1,2-Addition:

Results from this laboratory[13] show that changes in the butadiene-styrene ratio of charging, percentage conversion and type of modifier are without effect upon the mode of butadiene addition.

One effect of a slight change in the structure of the polymer has been noted, namely that copolymers of butadiene polymerized in the presence of cationic emulsifiers have a smaller vinyl-sidechain content.

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THE ADDITION OF THIO-ACIDS, MERCAPTANS, AND HYDROGEN SULFIDE TO UNSATURATED ALIPHATIC BONDS

I. INTRODUCTION.

Thio-acids, mercaptans, and H_2S add to aliphatic double bonds in the following manner, $-\overset{|}{C}=\overset{|}{C}- + HSQ \rightarrow -\underset{H}{\overset{|}{C}}-\underset{SQ}{\overset{|}{C}}-$ (i), where Q = H, an alkyl, aromatic, aralkyl, or an alkyl carbonyl radical. If the -SQ group attaches itself to the C atom, of an unsymmetrical double bond, containing the greater number of H atoms, the addition is termed "abnormal", assuming arbitrarily that these thio-compounds should add in the same way as the halogen acids according to the Markownikoff Rule. If the -SQ group attaches itself to the C atom containing the lesser number of H atoms the addition is termed "normal". The same analogy can be extended to triple bonds.

II. REACTIONS.

1. <u>Addition of HSH to alkenes</u>.--The addition of HSH to many olefins is normal at fairly high temperatures, under pressure in the presence of a catalyst, to produce mercaptans; the mercaptan formed in turn may react with another molecule of olefin to yield a thio-ether or sulfide

$$RCH{=}CH_2 + HSH \rightarrow R\underset{SH}{\overset{|}{C}}H_2-CH_3 \qquad \text{(ii)}$$

$$R\underset{SH}{\overset{|}{C}}HCH_3 + RCH{=}CH_2 \rightarrow R\overset{CH_3}{\overset{|}{C}}HS\overset{CH_3}{\overset{|}{C}}HR \qquad \text{(iii)}$$

Excess H_2S favors mercaptan formation, while excess ethylenic hydrocarbon favors sulfide formation. The ethylenic hydrocarbons employed are usually those obtained from petroleum distillation or cracking stills. The catalysts and temperatures employed include (a) organic peroxides with salts of strong acids, 100°,[9] (b) acid P compounds, 50-100°,[11] (c) a carboxylic acid anhydride plus a metal sulfide, 35-300°,[15] (d) Na in alcohol,[18] (e) S, 180° for 10 hr.,[26] (f) Fuller's Earth,[34] (g) silica gel, 600-700°,[37,38] (h) H_2SO_4, ordinary temperature[35] (i) Ac_2O plus NiS, 35-300°,[51] (j) NiS on kieselguhr 250-300°,[22] (k) H_3PO_4 on activated charcoal,[24] and (l) Ni on kieselguhr, 200°.[24]

At 200° over a Ni-kieselguhr catalyst and at space velocity 2, HSH reacts with propene to give 17% of a mixture containing ca. 65% iso-PrSH and 35% n-PrSH; H_3PO_4 on activated charcoal, and bentonite are also good catalysts.[24] Ni on kieselguhr was found the best catalyst for the conversion of $CH_2{=}CH_2$.[24] HSH reacts with tertiary base olefins at lower temperatures and

pressures.[2] Thus, $CH_2=C(CH_3)_2$, $(CH_3)_2C=CHCH_3$, and $CH_2=C(CH_3)C_2H_5$ are converted to tert-BuSH and tert-AmSH at 25-175° and 1-4 atmospheres pressure in the presence of a catalyst consisting of the acids and thio-acids of P and their anhydrides such as H_3PO_4, H_3PO_3, P_2O_5, P_2O_3, H_3PS_4, P_2S_5, or P_4S_3, supported on charcoal. The process may be used to produce mercaptans or to remove these tertiary base olefins from hydrocarbon mixtures. The above reaction can be reversed by heating the mercaptans at 300-450° in contact with H_3PO_4 on charcoal and the H_2S recycled.[3] 1,3-Butadiene can be purified by this method.[5]

HSH will add to pinene or turpentine in the presence of acidic or basic catalyst, such as H_2SO_4 or $Ca(OH)_2$, H_3PO_4 or $(CH_3)_2SO_4$, metallic Al, or metal sulfides, (24-60 hr. at 22-40°) to form mercaptans suitable as ore flotation agents or for the production of sulfonic acids or trithiocarbonates (wetting agents, etc.).[53] HSH will add to rosin under non-oxidizing conditions at ca. 80° to produce ore flotation agents.[54]

Compounds of the formula $RCH=CH_2$ and $ROCH=CH_2$ (R=H or an aliphatic cycloaliphatic, aliphatic-aromatic, or heterocyclic residue, and, in the case of the 1st formula, an esterified -COOH group or a -CN group) react with H_2S in the presence of a solvent or diluent according to a patent claim.[18] If the reactants do not contain basic groups, substances containing basic groups are added; e. g. C_2H_4 is heated with a solution of Na in EtOH and H_2S led in to give Et_2S. Styrene plus HSH in BuOH gives ~~Ph~~CH_3 Ph $CH_2SCH_2CH_3$ Ph ~~Ph.~~

Higher temperatures (35-500°) and super atmospheric pressures cause the formation of saturated hydrocarbons.[32]

$$C_nH_{2n} + H_2S \rightarrow C_nH_{2n+2} + S \qquad \text{(iv)}$$

$$C_nH_{2n} + H_2S \rightarrow C_nH_{2n+1}SH \qquad \text{(v)}$$

$$C_nH_{2n} + 2\ C_nH_{2n+1}SH \rightarrow (C_nH_{2n+1})_2S_2 + C_nH_{2n+2} \qquad \text{(vi)}$$

Ethylenic hydrocarbons react with H_2S at high temperatures and pressures in the presence of Ac_2O and NiS to form mercaptans, sulfides, and saturated hydrocarbons.[51] Thus, isooctane is prepared from diisobutylene at 250-300°, and sulfides from olefins at 35-300°. H_2S reacts with ethylenic hydrocarbons at 600-700° over silica gel to give mercaptans, sulfides, CS_2, thiophene, and thiophene derivatives of unknown structure.[37]

Originally it was thought that HSH added to olefins only in the normal fashion. Vaughan and Rust[1] discovered that HSH added abnormally to 1-butene, propylene, $ClCH=CH_2$, and 2-chlorobutene in the liquid phase under the influence of ultraviolet light (2800 A.) at low temperatures (ca. 0°). The

yields are high, and the product is mainly mercaptan plus some sulfide. With diallyl or dially ether, high molecular weight compounds are formed (mol. wt. ca. 250). A chain mechanism is postulated for the ultra-violet addition.

2. Mercaptans with Alkenes.--Mercaptans add to olefinic double bonds in the abnormal manner, in the presence of O_2 and peroxides. The reaction is inhibited by hydroquinone and piperidine, and accelerated by light. Special catalysts, such as sulfur,[19] Ni, Co, or Fe sulfides,[31] 75% H_2SO_4,[19] or 20% H_2SO_4 in AcOH,[19] are required to produce the normal addition. Ordinarily only relatively low temperatures (ca. 25 to 100°) are required for either addition. Jones and Reid[25] carried out their reactions with S catalyst at 180° for 10 hr. in a sealed bomb. The mercaptan-alkene reaction is very general. Posner[67] found that PhSH and $PhCH_2SH$ would add to a large number of solid and liquid olefins, the only exceptions noted being stilbene and 1,4-diphenylbutadiene. Since then the reaction has been applied widely. Reference to table I will give an idea of its applicability. Olefins will add mercaptans abnormally also under the influence of metal alkyls and ultra-violet light.[8] Diisobutylene reacts with an aliphatic mercaptan, containing >4 C atoms, at 200-500° under pressure to give isooctane.[51] At 35-200°, isobutylene plus tert-BuSH yields $(tert\text{-}Bu)_2S$.[51] Disulfides, formed by the oxidation of mercaptans, are converted to dienes at 400-700° with or without a catalyst.[47]

Dithiols will react with dienes to yield polymers. In a commercial process,[6] the reactants are sealed in a suitable container and exposed to a Hg arc, or 100-50°, or both until the polymerization has proceeded to the desired stage. Dithiols such as m-benzenedithiol, $HSCH_2CH_2SH$, or 1,10-decanedithiol, and dienes, such as, butadiene, vinylcyclohexene-3, cyclopentadiene, isoprene, divinyl formal, divinyl acetal, etc., are employed. Either can contain hetero-atoms such as O, S, and tert-N in the chain. The polysulfides can be oxidized to polysulfones, or converted to polysulfonium derivatives useful in the treatment of textiles or as corrosion inhibitors in lubricating oils.

Unsaturated mercaptans can polymerize with themselves. Thus, Allyl, cinnamyl, furfuryl, 2-butenyl, and 3-butenyl mercaptans cannot be prepared in the pure form because of the ease with which they polymerize. $(CH_3)_2C{=}CHCH_2SH$, $CH_2{=}CHCH_2CH_2CH_2SH$, and 1-cyclopentenyl mercaptan are much more stable.[25]

The ready addition of $HSCH_2CO_2H$ to many olefinic compounds and the easy estimation of the sulfhydryl group have led to the use of this reaction for the determination of the degree of unsaturation in oils, fats,[75] and gasoline.[48]

3. Thio-acids with alkenes.--The only thio-acid investigated was AcSH. It adds readily to aliphatic double bonds, in the absence of added catalysts, contrary to the Markownikoff Rule.[21,46]

$$PhCH{=}CH_2 + AcSH \xrightarrow{\text{room temp. 1 day}} PhCH_2CH_2SAc.$$

4. With α,β-unsaturated aldehydes, ketones, acids, keto-acids and esters.--Alkyls, aralkyl, and aryl mercaptans, and AcSH add normally in all cases to the α,β-double bond of compounds containing the aliphatic grouping: $-\overset{|}{C}{=}\overset{|}{C}-\overset{O}{\overset{\|}{C}}-$ (cf. 12, 14, 16, 45, 49, 50, 60, 65, 66). The reaction is catalyzed by both acids (HCl in AcOH)[65,66] and bases (NaOEt or piperidine)[49,50] and usually takes place on standing at room temperature. With an acid catalyst, mercaptole formation also takes place.[65] Apparently the reaction is entirely general and has been carried out with a large number of compounds, and is a 1,4-addition.[71] Thus,

$$PhCH{=}CHCOCH_3 + PhSH \xrightarrow[\text{piperidine}]{\text{2-3 drops}} PhC(SPh)HCH_2COCH_3 \qquad \text{(vii)}$$

$$CH_2{=}CHCOOH + AcSH \rightarrow AcSCH_2CH_2COOH \qquad \text{(viii)}$$

Kaneko and Mii[45] effected the addition of MeSH to acrylic and maleic acids, and to acrolein in the presence of a Hg salt, O_2, and light. The thioacetates formed, by a reaction of the type (viii) above, can be saponified with 12% NaOH to form a β-mercapto-acid. In a commercial process,[16] thiophenol, thiocresol, or a substituted thiophenol is added to an ester of acrylic, or α-alkacrylic acid, and exposed to a 150 watt bulb for 1 week to produce compounds suitable for use as plasticizer's and modifying agents for synthetic resins, cellulose derivatives, and the like, and of possible use as insecticides, rubber vulcanization accelerators, etc.

If the compound contains the grouping, $-\overset{|}{C}{=}\overset{|}{C}-\overset{O}{\overset{\|}{C}}-\overset{|}{C}{=}\overset{|}{C}-$, 1 or 2 mols mercaptan may be added.[49] If it contains the grouping, $-\overset{|}{C}{=}\overset{|}{C}{=}\overset{|}{C}{=}\overset{|}{C}-\overset{O}{\overset{\|}{C}}-$, only one mol mercaptan adds.[49]

Only two examples of HSH addition to α,β-unsaturated keto-compounds were found. One is a commercial process[12] for producing thiols which involves reaction of an α,β-unsaturated ketone with HSH in the presence of piperidine in a closed system at a temperature between 20° and the decomposition temperature of the products. (Also, cf. Example No. 21, Table I.)

5. With α,β-unsaturated sulfones and sulfoxides.--Mercaptans, in the presence of a base, add normally to the double bond of α,β-unsaturated sulfones[61,52] or sulfoxides.[52] Elevated temperatures are not needed. Thus, $PhCH{=}CH_2SO_2PhCH_3$-p plus p-CH_3PhSNa in C_6H_6 gives $PhCH(SPhCH_3)CH_2SO_2PhCH_3$ on standing

TABLE I

EXAMPLE NO.	ALKENE Amount	MERCAPTAN Amount	CONDITIONS, YIELD, PRODUCTS	TYPE ADDN.*	REF.
1	1-Butene 0.044 mol	HSH 0.088 mol	0°, 4 min., u. v. light. 80% reacted, 85% BuSH + 15% Bu_2S	A	1
2	$CH_3CH{=}CH_2$ 7.4 vol.	HSH 7.4 vol.	0°., 6 min., u. v. light $PbEt_4$, 75% reacted, 80% PrSH + 20% Pr_2S.	A	8
3	$CH_2{=}CHCH_2COOH$ 40 g.	AcSH 41 g.	40°, 75 min., 64 g. product	A	14
4	$CH_3CH{=}CH_2$	PhSH	No catalyst, Air present, 8 hr., 120°, 60% yield.	A	19
5	$(CH_3)_2C{=}CHCH_3$	PhSH	20% H_2SO_4 in AcOH, room temp., 80% yield	N	19
6	$CH_3CH{=}CH_2$ 21 g.	HSH 17 g.	180° for 10 hr. in sealed bomb, S catalyst, 7% iso-PrSH, 90% iso-Pr_2S	N	20
7	$CH_3(CH_2)_8CH{=}CH_2$	B-$C_{10}H_7SH$	180° for 10 hr. in sealed bomb, S catalyst. Alkene peroxides present.	A	20
8	$CH_3CH{=}CH_2$ 0.35 mols	EtSH 0.25 mols	4 hr. at 100°, air present, metal sulfide (?), 64% yield EtSPr-n	A	21
9	iso-Butene 0. 28 mols	n-BuSH 0.11 mols	2 hr. at 100°, air and metal sulfide (?), 66% yield n-BuSBu-i	A	21
10	$(CH_3)_2CHCH{=}CH_2$ 0.17 mols	AcSH 0.126 mols	3 hr. at 100°, air present, metal sulfide (?), 86% yield AcSAm-i	A	21
11	$(CH_3)_2C{=}CHCH_3$ 0.42 mols	AcSH 0.33 mols	4 hr. at 70°, air present, metal sulfide (?), 86% yield AcSAm-i	A	21
12	PhCH=CHCOPh Equimolecular	$PhCH_2SH$ or p-$CH_3C_6H_4SH$	No catalyst, 5 min. at 100° gives quite complete reaction.	N	24
13	$PhCH{=}CHCOOCH_3$ Equimolecular	$PhCH_2SH$ or p-$CH_3C_6H_4SH$	2 hr. at 100°, 0.1 cc. piperidine, Good yield. No reaction sans piperidine.	N	24
14	$CH_3CH{=}CH_2$ 8 g.	PhSH 20 g.	180°, 10 hr. in sealed bomb, 1 g. S catalyst, 12 g. i-PrSPh.	N	20

TABLE I (cont'd)

EXAMPLE NO.	ALKENE Amount	MERCAPTAN Amount	CONDITIONS, YIELD, PRODUCTS	TYPE ADDN.*	REF.
15	$PhCH{=}CH_2$	$HSCH_2COOH$	Ascaridole catalyst-immediate reaction. Antioxidant conditions-no reaction.	A	41
16	$CH_2{=}CHCH_2OH$	CH_3SH	$(CH_3)_2Hg$ or $(AcO)_2Hg + O_2$ + light, 93% yield.	A	42
17	$CH_2{=}CHC{\equiv}CCH{=}CH_2$ 1 mol	p-$CH_3C_6H_4SH$ 2 mols	10 days, room temp., 1 mol mercap-adds at each -C=C-. Accelerated by light, Hg arc-5 hr., 80% yield.	A	56
18	$PhCH{=}CH_2CO{-}CH{=}CHPh$ 2.2 g. 2.0 g.	PhSH - 1 g. - 2 g.	2-3 drops piperidine, C_6H_6 solvent, room temp., immediate reaction, 1 or 2 mols PhSH add.	N	47
19	$PhC{\equiv}CCOC_6H_4OCH_3$	PhSH	Same as above, product . $PhC(SPh){=}CHCOC_6H_4OCH_3$	N	50
20	$PhCH{=}CHCH{=}CHCOPh$	i-AmSH	Same as above, product is $PhCH{=}CHCH(SAm\text{-}i)CH_2COPh$	N	49
21	$PhCH{=}C(COCH_3)_2$	HSH	NaOEt catalyst, slightly warm in alcohol, product is PhCHS		49
22	$PhCH{=}CH(COCH_3)_2$	i-AmSH	NaOEt catalyst, room temp.	N	49
23	$CH_3(CH_2)_{10}CH{=}CH_2$	$HS(CH_2)_nSH$ n=2 to 12,18	10 hr. at 180° in sealed bomb, alkene peroxide catalyst, $CH_3(CH_2)_{12}$-$S(CH_2)_nS(CH_2)_{12}CH_3$ nearly quantitatively, except when n=18.	A A	20 20

*A = Abnormal, N = Normal

several days at room temperature.[61] A commercial process[52] employes $CH_2=CHSO_2R$ or $CH_2=CHSOR$ (where R may be any one of a wide variety of organic radicals) and any one of a large variety of mercaptans containing at least one -SH group, in the presence of a basic catalyst such as NaOEt, or NaOMe. The products may be used as dye intermediates, in some cases as dyes, as assistants in the textile industry, or for combating vegetable and animal pests.

6. With Acetylinic Bonds.--Vinyl sulfides are formed by the reaction of HC≡CH with mercaptans at 50-300° in the presence of basic oxides or salts.[56,58] Thus, PhSH + HC≡CH(dild. with N_2) $\xrightarrow[160^\circ \quad 15\ atm.]{BuOH + KOH}$ $PhSCH=CH_2$. Other compounds made in this way include p-thiocresol vinyl ether, 2-vinylmercaptobenzothiazole, $PhSCH_2CH_2SPh$, ethanedithiol di-p-tolyl ether, 1,8-chlorothionaphthol vinyl ether, and $CH_2=CHSC=CHC(CH_3)=CClCH=CCH_3$.

Three processes are patented for producing thiophene from HC≡CH and H_2S. Passing a mixture of H_2S and HC≡CH over bauxite at 320° is said to give practically pure thiophene;[39] over $Ni(OH)_2$ on cement at 300°, a mixture of products, from which mercaptans, thiophene, and methyl thiophene may be fractionated, is obtained.[39] In another process,[10] thiophene is made by passing HC≡CH + H_2S in the ratio 4:3 to 2:3, over a catalyst containing at least one sulfide of Pb, Mn, Cu, Sn, Mo, Co, or Ni on a porous support such as alumina at 500-750° under anhydrous conditions.

α-Trithioacetaldehyde is formed by the reaction of HC≡CH with an aqueous solution of H_2S at 100°, 10-20 atm. pressure, in the presence of a small amount of KSH. A mixture of EtSH and $CH_2=CHSEt$ is obtained by passing H_2S and HC≡CH in a 1:1 ratio through diethylene glycol containing KSH. By using excess HC≡CH, $EtSCH_2CH_2SEt$ is the main product (cf. 17, 28, 29, and 30).

β-Alkylmercaptoacrolein dialkyl mercaptals are formed by treating a compound of the following formulas with an alkyl mercaptan, such as EtSH, in the presence of an acid condensing agent, such as H_2SO_4 or $ZnCl_2$ (a) $CH≡CCH(SR)_2$, (b) $CH≡CCH(OR)_2$, (c) $ROCH=CHCH(OR)_2$, or $RSCH=CHCH(OR)_2$. The R groups are alkyl groups such as Et.

III. THE MECHANISM OF THE REACTION.

1. The Abnormal Addition.--It has been clearly shown[41,42,20,43] that the abnormal addition of mercaptans to alkenes is catalyzed by O_2 and peroxides, that it is inhibited by hydroquinone and piperidine, and that it is accelerated by light. The peroxides formed on exposure to air are sufficient to catalyze the abnormal addition; careful purification of the reactants and exclusion of air prevents or greatly retards any addition. The structures of

the products formed supply excellent evidence that the addition does not proceed through a polar or ionic mechanism. The reaction is therefore postulated to be a chain reaction[55,43,42]

$$RSH + O_2 \text{ (or peroxide)} \xrightarrow{\text{alkene}} RS\cdot + HOO\cdot$$

$$RS\cdot + R'CH{=}CH_2 \rightarrow R'\dot{C}HCH_2SR \ (\Delta H{=}13 \text{ kg.-cal./mol})$$

$$R\dot{C}HCH_2SR + RSH \rightarrow R'CH_2CH_2SR + RS\cdot \ (\Delta H{=}0).$$

The effects of O_2, peroxides, light, and antioxidants, and the nature of addition products very closely resemble those observed in the abnormal addition of HBr. In both instances, the heats of reaction of the corresponding steps, as calculated from estimated bond energies,[70] are almost identical. The easy oxidation of mercaptans to disulfides and the suggested dissociation of disulfides into free radicals[72] further support the suggested mechanism. The fact that HSH and mercaptans add abnormally under the influence of ultra-violet light adds further evidence of a chain mechanism.

2. The Normal Addition.--Mercaptans add normally to olefinic double bonds conjugated with carbonyl groups. Such additions are catalyzed by both acids (HCl in AcOH) and bases (piperidine or NaOEt). The unilateral addition of mercaptans to such double bonds agrees closely with the behavior of HBr. It is apparently a 1,4-addition.[71]

A special catalyst is required in every case to bring about the normal addition of mercaptans to alkenes. The mechanism of the normal addition is unknown but several analogies to the normal addition of HX exist: (a) The catalysis by H_2SO_4 resembles the participation of 2 molecules of HX in the addition of one such molecule, and suggests that the alkene-acid complex reacts with RSH. (b) The catalysis by bases recalls the accelerating effect of NH_4^+ salts on HX additions, and suggests that SR^- ion may sometimes participate in the reaction. (c) Catalysis by S resembles the catalysis of HI addition by I_2. (d) Catalysis by metal sulfides is somewhat analogous to the catalysis of HX additions by metal halides.[55]

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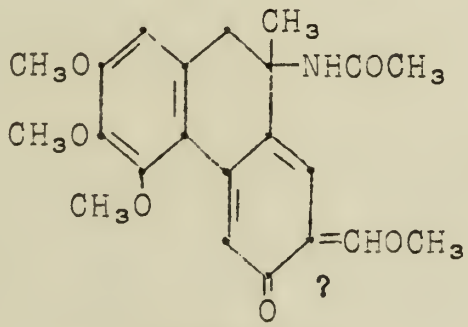
Reported by D. W. Hein
April 24, 1946

INVESTIGATIONS ON THE STRUCTURE OF COLCHICINE

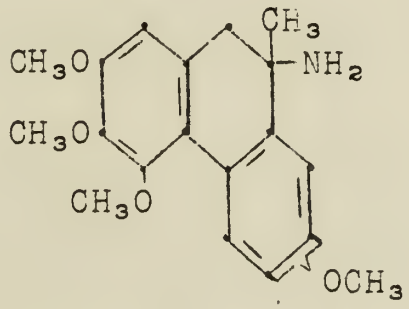
Cook, University of Glasgow, England

In a recent seminar (1) Dr. Frank discussed the structure of colchicine as it had been developed before 1940. Since that time, the investigations of Cook have resulted in serious objections to the ring structure previously proposed.

Windaus and other workers considered colchicine to have the phenanthrene ring system as shown below, the main evidence in



colchicine



colchinol methyl ether

favor of this structure being a degradation of colchinol methyl ether by exhaustive methylation, demethylation, and distillation from zinc dust to give 9-methylphenanthrene. This series of reactions, it was thought, established the structure of colchinol methyl ether as a phenanthrene derivative, and thus that of colchicine.

After critical consideration of the proposed structure for colchinol methyl ether, Cook (2,3,4) raised his first objection on the grounds that the substance gave no indication of the expected easy loss of ammonia to form a phenanthrene. Furthermore, treatment of the amine with nitrous acid gave a carbinol which showed behavior incompatible with that expected of a hydroxydihydrophenanthrene, again because of the impossibility of aromatization.

The first alternative structure, with the amino group on the methyl group, was eliminated on the basis that the acetyl derivative was unchanged after treatment with platinum black at 280°. Neither could an aldehyde or acid oxidation product be obtained. In an effort to determine the nature of the hydroxyl group, the carbinol was treated with phthalic anhydride. No reaction was obtained in benzene solution, but fusion at 180° gave an acid phthalate - behavior characteristic of a secondary carbinol (5). No indication of any phenanthrenes formed by the dehydrogenating action of nitrous acid was found by ultraviolet.

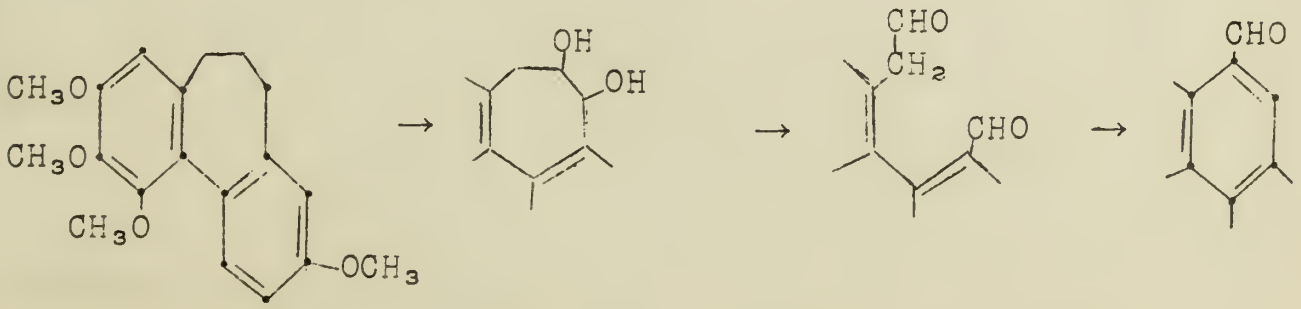
Cook now considered the Windaus structure sufficiently inconclusive to warrant synthesis of the tetramethoxy derivatives expected in the degradation of colchinol methyl ether. The two

possibilities are 2,3,4,6- and 2,3,4,7-tetramethoxy-9-methylphenanthrene. The phenanthrene-9-carboxylic acids were prepared by a Pschorr type reaction, and the carboxyl groups converted to methyls by McFayden-Stevens reduction to aldehydes followed by Kishner reduction. The use of homoanisic acid gave an unequivocal synthesis with a 6-methoxyl, while m-methoxyphenylacetic acid gave two series of compounds which resulted in both the 5- and 7-methoxy derivatives. The natural degradation product was shown by mixed melting point to be identical with none of these. Two chemical differences were noted between the deaminocolchinol and the synthetics; 1) the natural product gave no picrate, as contrasted with the synthetics, and 2) deaminocolchinol was easily reduced to a dihydro compound under conditions where the others were unaffected. This dihydro derivative could not be dehydrogenated with Pd or Se.

In the dehydration of the carbinol, two products are obtained, deaminocolchinol methyl ether and isodeaminocolchinol methyl ether. Both of these substances give the same dihydro compound, and they resemble each other in lack of aromaticity in the B ring. The only explanation on the basis of a 6-member ring involves the fusion of a cyclopropane ring, a very unlikely system.

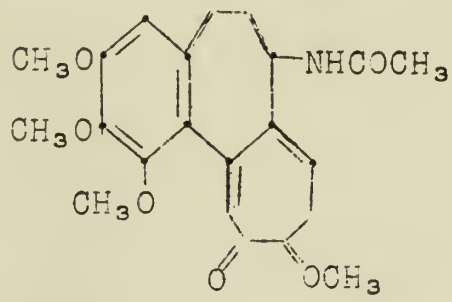
Although the assignment of a 7-member ring to colchicine may be premature, this arrangement explains the chemical properties of its degradation products satisfactorily. Windaus's degradation utilized reactions for which it has not been shown that rearrangements cannot occur. The oxidation of a 7-member ring to a quinone is not without precedent (6). An intermediate triketone could lose CO easily, or the oxidation may take another path. This quinone product is accompanied by another product which has the properties of an α,β-unsaturated ketone.

Cook investigated the controlled oxidation of the olefinic center in deaminocolchinol methyl ether, and found that OsO_4 in ether gave a glycol which could be split by lead tetraacetate to a gum. This gum slowly crystallized to give a 9-phenanthraldehyde, and the solidification was greatly accelerated by the addition of a trace of sodium carbonate. The reactions proposed by Cook are shown below. The isolation of succinic



acid from colchicine oxidation by Windaus is an indication that the 7-member may be present in the parent compound.

It is interesting to note that Dewar (7), reasoning by analogy to stipitatic acid, has recently proposed that colchicine has two 7-member rings. He has no experimental evidence, but proposes the structure shown below.



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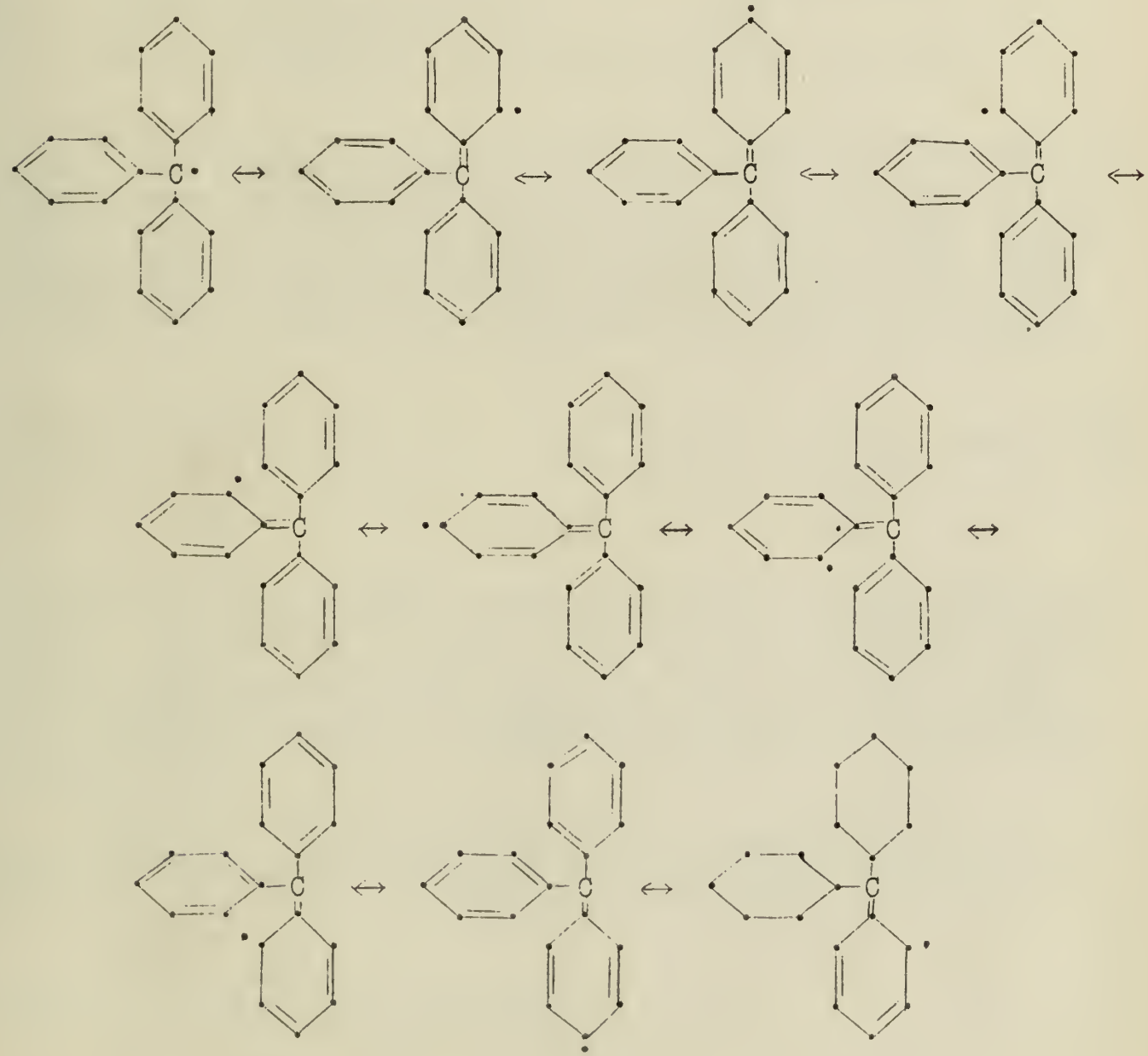
Reported by Ben F. Aycock, Jr.
May 1, 1946

RESONANCE AND THE THEORY OF COLOR

After the development of the concept of resonance, it was observed that many colored organic compounds were best represented as a composite hybrid derived from a relatively large number of resonance forms. For example the free electron in the triphenylmethyl free radical can occupy ten different positions in the molecule.

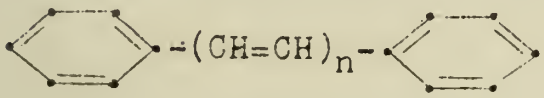


It is to be noticed that the free radical so formed is orange yellow, while the parent hexaphenylethane in which such resonance forms are impossible, is colorless. If our assumption that resonance is the principal cause of color is correct, we would expect that free radicals in which the phenyl group has been replaced by napthalene or biphenyl would be more highly

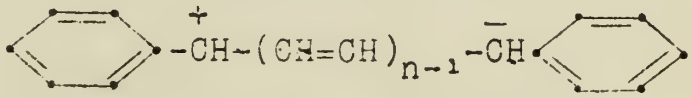
colored than that of triphenylmethyl since these substitutions will increase the number of resonance forms of the free radical. This is verified by the following chart.

Free Radical	Color
Triphenylmethyl	Orange-yellow
Diphenyl-p-biphenylmethyl	Orange-red
Phenyldi-p-biphenylmethyl	Red
Tri-p-biphenylmethyl	Red
Phenyl-p-biphenyl-α-napthylmethyl	Deep red-brown

In order for the resonance hybrid to absorb light, one or more of the possible structures must be ionoid in character. Thus benzene, although greatly stabilized by the Kekulé resonance forms is not able to absorb light in the visible region of the spectrum since neither of these forms has ionic character. In the diphenylpolyenes, consideration must be given to the ionic resonance forms such as IIb. The observed bond



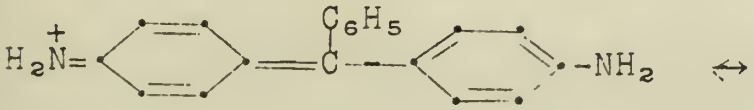
IIa



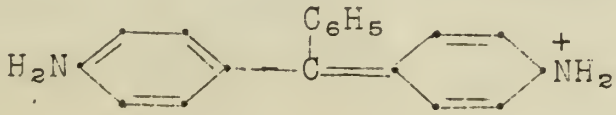
IIb

distances in the polyenes offer confirmation to such resonance forms. The carbon atoms in the polyene chain are alternately spaced 1.37 and 1.41 A. apart. This is to be compared with the normal single bond distance of 1.54 A° and the normal double bond distance of 1.34 A. Lengthening the polyene chain causes the absorption spectra to be shifted toward the red portion of the spectrum.

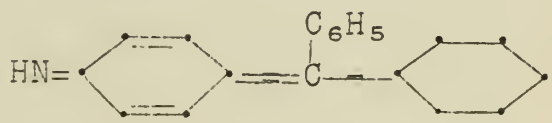
Doebner's violet (hydrochloride of p,p-diaminotriphenyl carbinol) may be represented by the two extreme resonance hybrids IIIa and IIIb. In contrast fuchsonimine (IV) cannot



IIIa



IIIb

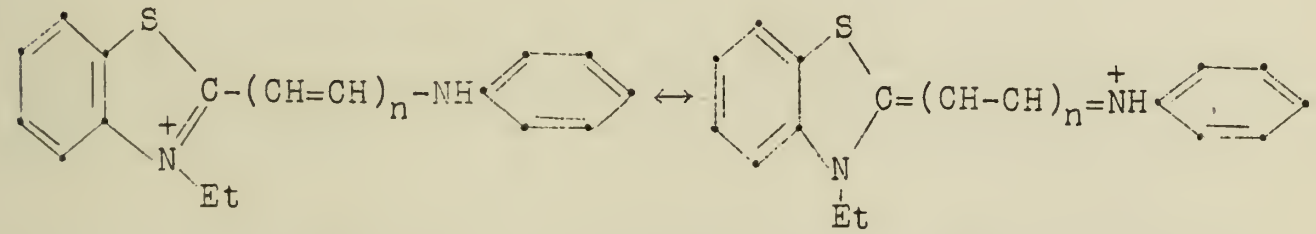


IV

possess analogous resonance hybrids and is colorless, though it contains the same chromophoric group as Doebner's violet. The amino groups in Doebner's violet may be monoalkylated or dialkylated without appreciably altering its color. Trialkylation, however, forces the retention of the positive charge on one amino group, thus preventing resonance of the type found in the parent dye. Trialkylation, in general, is found to render chromophoric amino groups ineffective.

Resonance of a similar type occurs in the cyanine dyes.

Fisher and Hamer have shown that in an unsymmetrical dye of the cyanine type, the frequency at which maximum absorption takes place is the mean of the frequencies of the parent symmetrical dyes provided the two halves of the molecule possess the same basicity. For example the unsymmetrical cyanine V resonates between the structures Va and Vb; its maximum absorption is at



Va Vb

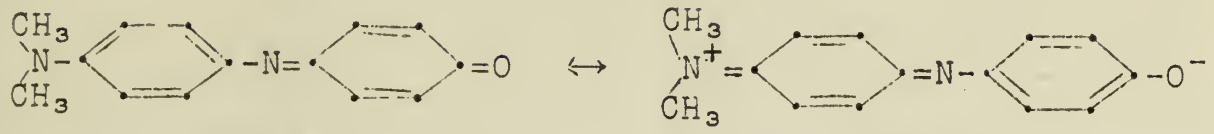
5160 A°. The mean of the frequencies of absorption of the parent dyes VI and VII is 5210 A°. This near agreement between the calculated and observed frequencies of maximum absorption signifies that the extent of resonance in the unsymmetrical dyes is approximately as great as in the symmetrical parent dyes. If the two halves of the cyanine dye differ markedly in basicity, the deviation between the calculated and observed value of maximum frequency is great.

The acetyl derivatives of V are in every case lighter in color than the corresponding anilino compounds. The basicity of NHC_6H_5 group in the latter is greatly reduced by acetylation. This minimizes the contribution of the acetyl derivative of Vb inasmuch as it is hardly basic enough to compete successfully for the positive charge.

The dependence of color upon the solvent is shown in the

VI VII

case of phenol blue. The principal resonating structures are shown (VIIIa and VIIIb). Structure VIIIb makes only a small



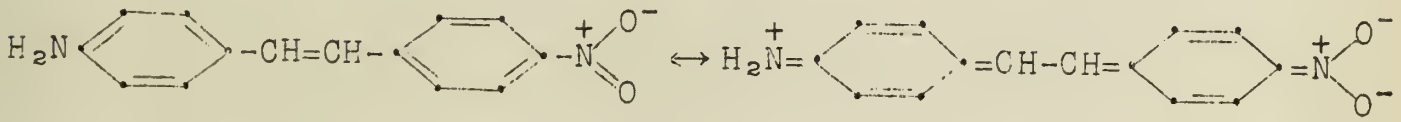
VIIIa VIIIb

contribution to the hybrid form in a nonpolar solvent. It is not as stable as VIIIa by reason of the separation of its charges. On the other hand, in a polar solvent, VIIIb will be stabilized by the interaction of the electronic charges and the dipolar solvent molecule. That this is the case is shown in the following table.

Solvent	Color	Dielectric Constant	λmax. obs.	λmax. calcd.	Δλ
Cyclohexane	red violet	2	5520		
Acetone	violet	21	5820	6825	1005
Methyl Alcohol	blue violet	31	6120	6805	685
Water	deep blue	80	6680	6745	65

It is to be noticed that when VIIIb is stabilized, each resonance form makes approximately the same contribution to the hybrid structure, and the value of λ max. approaches that of the calculated value.

The cyanine dyes have nitrogen atoms linked by an odd number of carbon atoms. If we compare the cyanines with the compounds containing nitrogen atoms linked by an even number of carbon atoms, we find that the cyanines are highly colored while the other class of compounds are scarcely colored at all..



IXa IXb

Although the conjugated chain in compound IX is very long and is provided with the necessary terminal auxochromic atoms, it nevertheless scarcely absorbs beyond the ultraviolet, which may be correlated with the fact that in the second extreme configuration IXb both benzene rings are quinoid and there is a strong tendency to remain as IXa.

When light is absorbed by an organic molecule, the molecule becomes activated; presumably the quantum of energy from a photon of light gives rise to polarization of the molecule.

For an olefinic double bond, such large amounts of energy are needed that only ultraviolet radiation has sufficient energy to bring about activation. (The transformation of trans compounds to their cis isomers by the action of ultraviolet light is related to this activation.) In the polyenes, the ionic resonance forms permit activation with light of lower energy--that is with light in the visible spectrum. Here the absorption is mainly in the blue portion of the spectrum; therefore, the compound appears yellow to red due to the fact that these wave lengths of light are transmitted unchanged. Lengthening of the chain permits still easier polarization (this lengthening increases the number of permissable resonance forms) and absorption takes place at still longer wave lengths.

Similar processes of reasoning can be applied to the other major types of dyes. We can say at present that our ideas of resonance can offer at least an approximate answer to the question of color.

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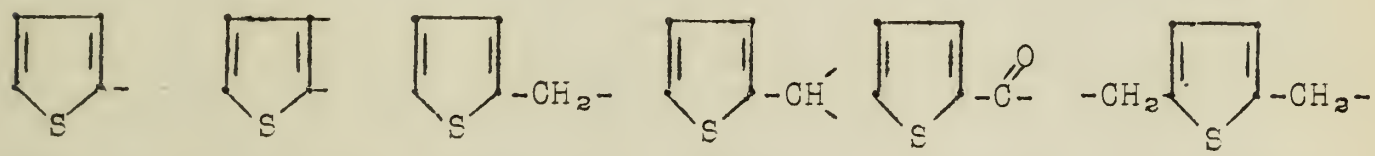
Reported by Herschel Porter
May 1, 1946

THIOPHENE

Thiophene is found in benzene obtained from coal tar in amounts ranging from 0.1 to 0.5 percent. It is very similar to benzene in physical and chemical properties, being in general somewhat more reactive.

Thiophene is prepared in the laboratory by heating anhydrous sodium succinate with phosphorous trisulfide in an atmosphere of carbon dioxide (1). Other preparations are extremely numerous and usually consist in passing an olefin over a sulfide at temperatures of 300 to 800 degrees. Most recent patents describe the preparation of thiophene from acetylene and hydrogen sulfide in the presence of lead or manganese sulfides at elevated temperatures. The yields are described as good (2). The present availability of thiophene at low prices is due to a new commercial synthesis, probably from butane and sulfur.

Thiophene possesses the characteristics of an aromatic compound. Its resonance energy, 31 k.cal per mol (3) lies between that of benzene and furan. The sulfur cannot be oxidized to a sulfone nor will it form an addition compound with alkyl halides. Many position isomers of substituted thiophenes show the unhappy property of having identical melting points, and mixed melting points show no depression. This difficulty is encountered even in the melting points of thiophenes and analogously substituted selenophenes. The following nomenclature is used in the thiophene series.



thienyl thienylene thenyl thenal thenoyl thioxal

The thiophene ring is quite stable, but it can be cleaved either by strong oxidizing or reducing agents. It can be distilled from sodium, but potassium will break the ring giving potassium sulfide and the salt of an unsaturated acid. The double bonds are not affected by ozonized air, but treatment of a suspension of thiophene with ozonized oxygen gives the ozonide which decomposes explosively to give glyoxal. Hydrogen peroxide reacts to give a di- and a tetraoxide in which the oxygen molecules seem to be on the sulfur atom (4). Oxidation with oxides of nitrogen, permanganate, hypochloride, thallium hydroxide or by an electrolytic process leads to scission of the ring. Attempts to reduce the double bonds to obtain the di- or tetrahydro derivatives give paraffins or mercaptans.

Substitution goes almost exclusively in the alpha position. This is true even in negatively substituted derivatives; for example, 2-nitrothiophene gives mostly 2,5-dinitrothiophene on

further nitration. In a rough way the 2,4 positions correspond to the meta positions in benzene, and the 3,4 to the para in that they are the highest melting isomers. Substituents in the alpha positions are quite labile and are often removed or replaced during reactions.

Because of its greater activity, reactions which proceed rapidly with benzene may destroy thiophene entirely, this is especially true of reactions involving anhydrous aluminum chloride. Thus neither the Gatterman synthesis of aldehydes nor the formation of amides by the action of chlorocarbamate on thiophene is successful. The Diels-Alder reaction fails with thiophene, a fact which might seem surprising by analogy to pyrrole. The reaction with diazoacetic ester proceeds more slowly than in the case of benzene but the product is obtained in fair yields.

The reaction of thiophene with mercuric chloride or acetate is very important in the synthesis of derivatives since the mercuri group is readily replaced by halogens or acyl radicals. The halogen derivatives react normally; they will form Grignard reagents even in the beta position and through these the acids are made. All possible mono and polybasic acids are known. They are slightly stronger acids than the corresponding benzene derivatives and show no tendency to form anhydrides. They may be converted to the usual acid derivatives such as amides or nitriles, and the acid chlorides may be used in Friedel-Crafts reactions (5). The aldehydes cannot be made by a Rosenmund reduction of an acid chloride, they are best made from the methyl ketone by oxidation to the glyoxylic acid then decarboxylation. All of the usual carbonyl derivatives can be made from the aldehyde and it will undergo the Cannizarro reaction in the presence of base. It will not form the analog of benzoin on treatment with potassium cyanide and these compounds seem to be unknown in the thiophene series (6). Thiophene mercaptan is obtained by the reduction of the sulfonic acid, it differs from thiocresol in that it will couple with diazonium salts. Thiophene-ols are unknown but 5-hydroxy-2methyl-thiophene (thiotenol) is well known and exists in tautomeric equilibrium with the keto form. Several other substituted thiophene-ols are known, all of which show this tautomerism. The amines may be prepared by reduction of the nitro compounds and are isolated as the complex with stannic chloride. In this form they are stable, but the free amines quickly polymerize to a "solid mass" on exposure to air. The amine is practically impossible to diazotize, indeed there is no direct evidence that it has ever been accomplished.

The di- and tetrahydrothiophenes are known although they cannot be made by direct reduction. They exhibit no aromatic character but react like aliphatic sulfides. By passing over platinum at 200 degrees they are converted to thiophene.

Many alkyl thiophenes are known. They may be made, among other ways, by the Clemmensen reduction of the ketones. Substitution of aryl radicals in the ring reduces the aromaticity so that 2,3,4,5-tetraphenylthiophene (thionessal) can be oxidized to a sulfone. The thienyl group confers more color on molecules than does the phenyl group, thus terthienyl is green-yellow and quarterthienyl is chrome yellow, where as the corresponding polyphenyls are colorless.

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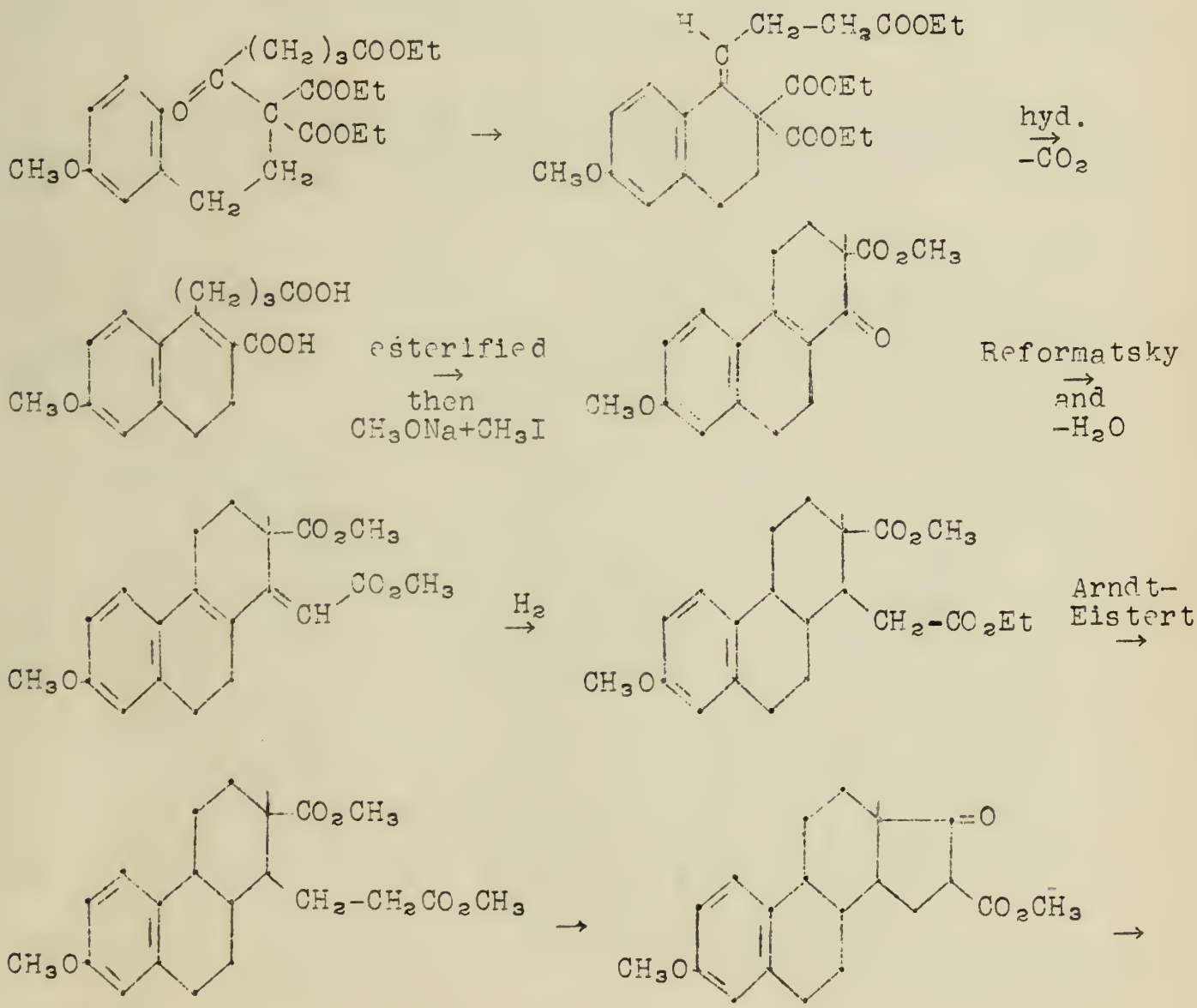
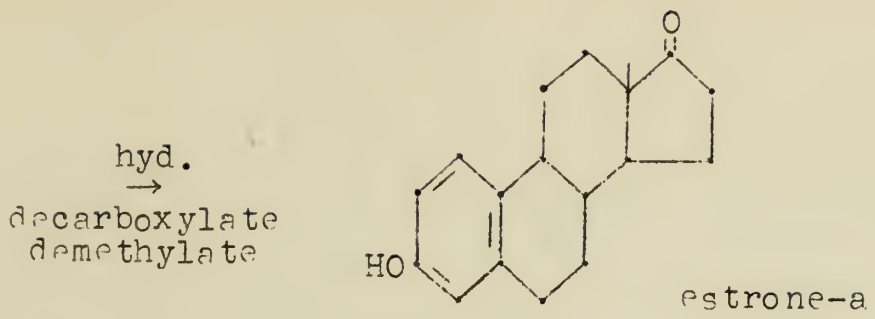
Reported by E. R. Trumbull
May 8, 1946

RECENT DEVELOPMENTS IN THE TOTAL SYNTHESIS OF STEROIDS

In this seminar an attempt will be made to show how far the total synthesis of steroids has progressed by giving examples which illustrate the approximate point of furthest advance in each of several general synthetic schemes.

A. Bachmann's Equilenin Method.--d-Equilenin is the only naturally-occurring steroid that has been synthesized and isolated in the pure form. Other steroids have been synthesized but not isolated in a pure form. The synthesis of dl-equilenin by Bachmann in 1940 was reviewed in this seminar by Boyd in the fall of 1943. Bachmann, Kushmer, and Stevenson attempted the synthesis of esterone but could isolate only an isomer in a pure state. From the final oily mixture was obtained a crystalline

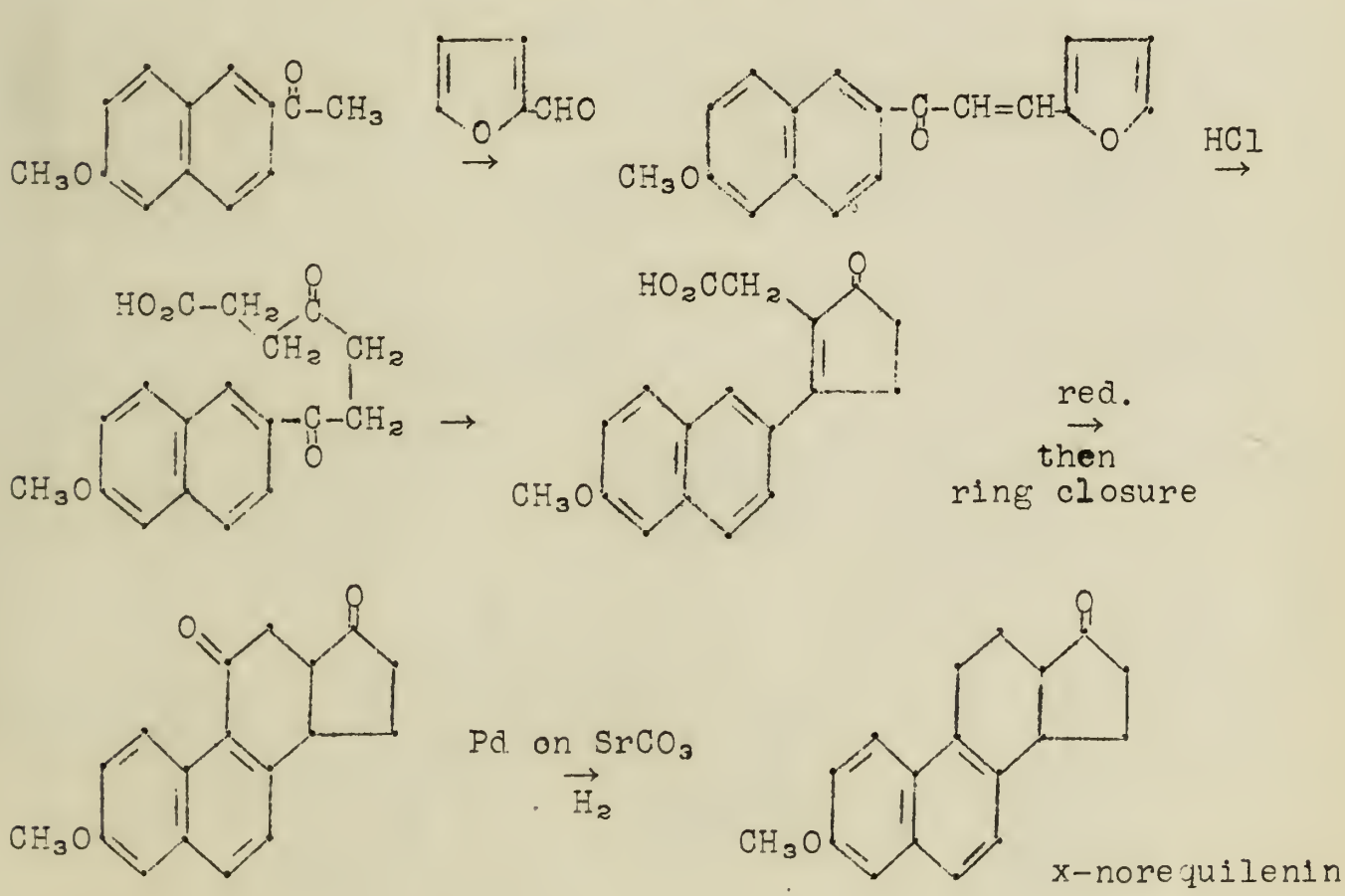




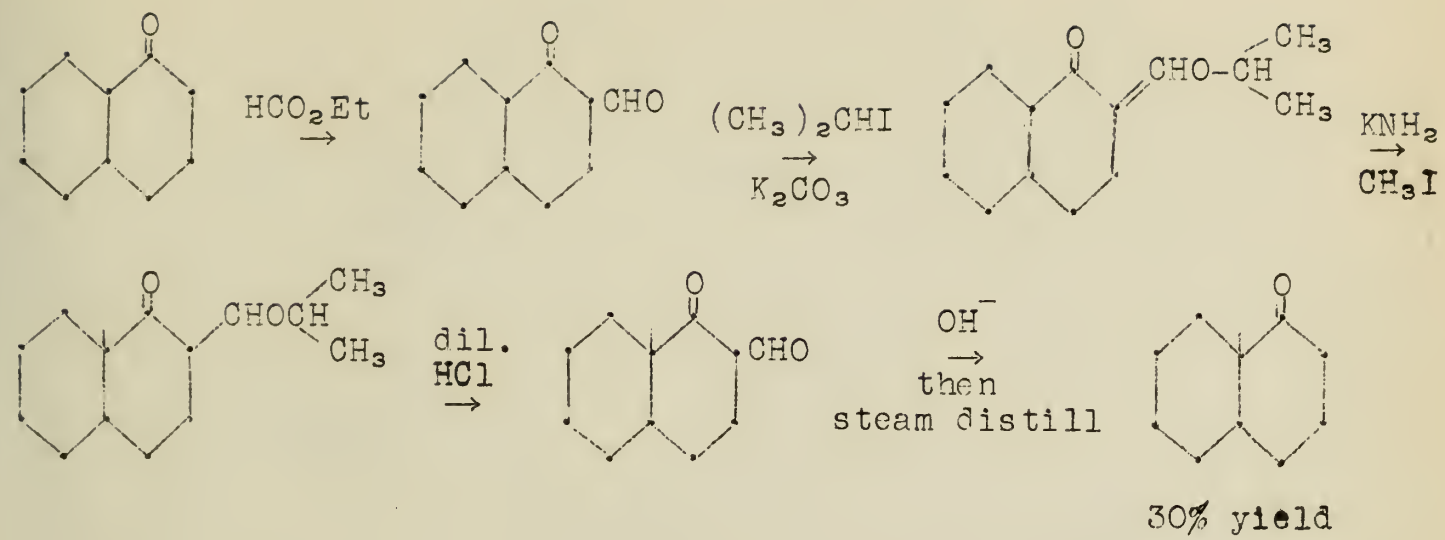
solid called estrone-a, which had 1/250 the activity of the natural substance.

Recently Johnson, Peterson, and Gutsche have shortened the number of steps necessary for the synthesis of equilenin by a simultaneous Stobbe condensation and ring closure on a β-keto nitrile. They are attempting to extend this synthesis to estrone.

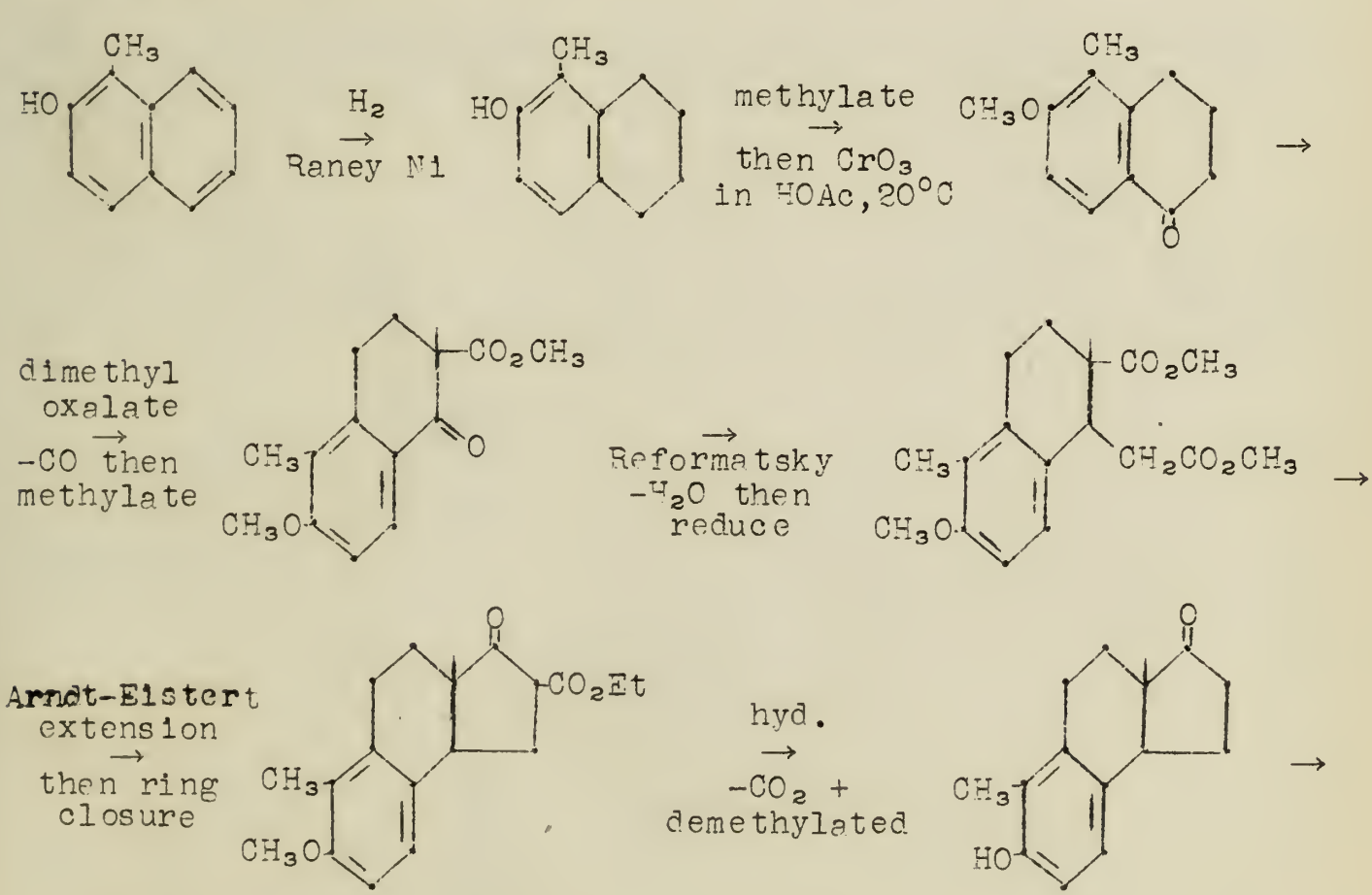
B. Robinson Diketone Method.--Robinson has synthesized x-norequilenin and x-norestrone by this method but was unable to introduce an angular methyl group in the 13-position.

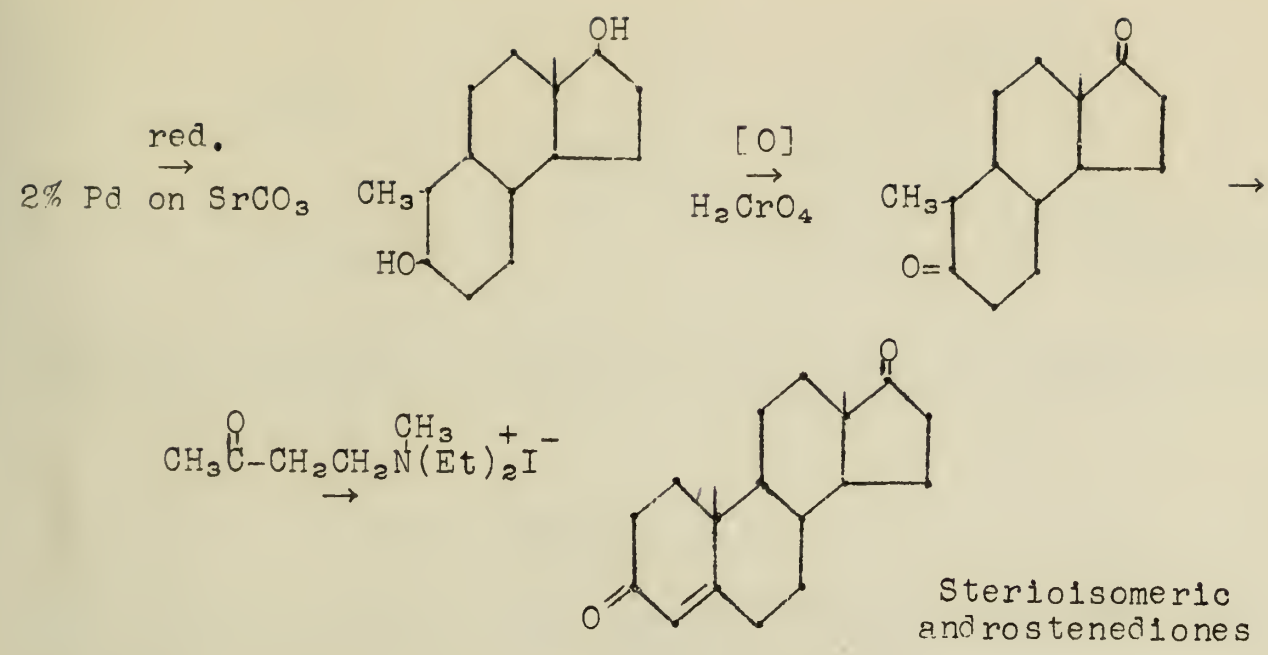


Johnson and Posvic may have increased the importance of this method by developing a convenient method for the introduction of an angular methyl group.



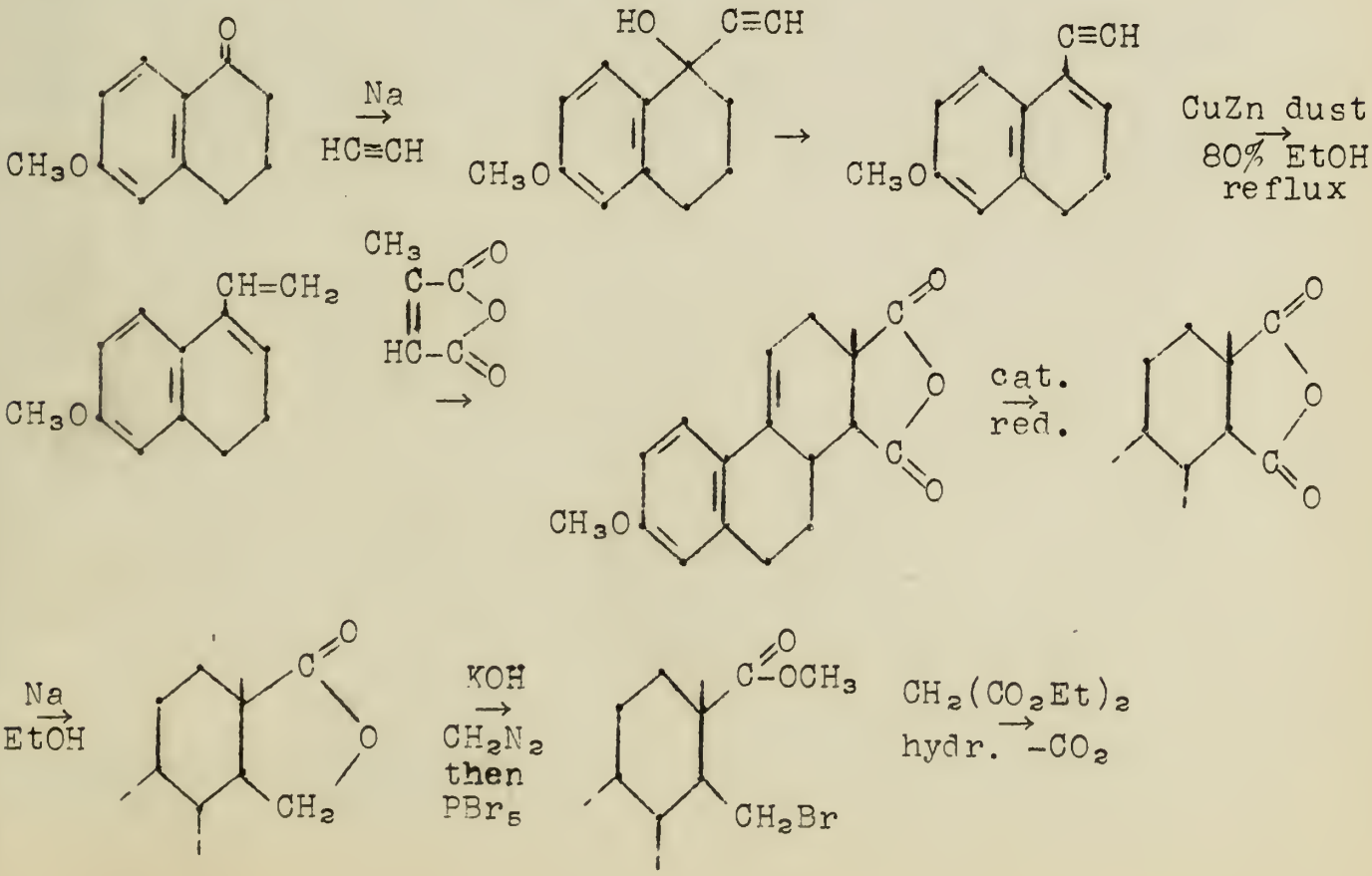
C. The Robinson-Mannich Base Method.--This is probably the best method for the synthesis of non-benzoid steroids. Martin and Robinson recently have applied the method to the synthesis of androstenedione.

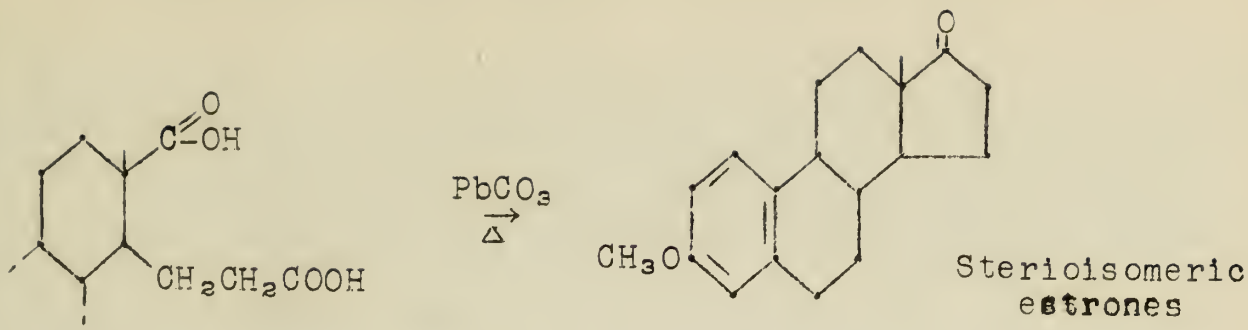




The testing of these compounds has not been reported as yet.

D. <u>The Diels-Alder Synthesis</u>.--Recently Breitner has modified a procedure of Dane for the synthesis of estrone using the Diels-Alder reaction. The mixture was shown to possess





estrogenic activity. Activity of a steroid is usually almost conclusive proof in structure determination.

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Reported May 8, 1946
by William J. Bailey

THE REACTION OF FORMALDEHYDE WITH PROTEINS

Formaldehyde reacts with proteins to form more or less stable compounds in which the original properties of the protein are profoundly altered. It was at one time thought that it might be due to the transformation of the original amino groups present in the protein molecule to Schiff bases. More recent evidence (1)

$$-NH_2 + HCHO \rightarrow -N{=}CH_2 + H_2O$$

favors a simple addition reaction, leading to methylol or dimethylol compounds. However, the marked decrease in hydrophilic

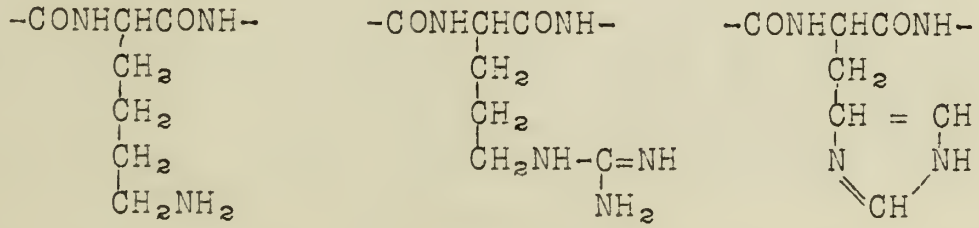
$$-NH_2 + HCHO \rightarrow -NHCH_2OH \xrightarrow{-HCHO} -N\begin{matrix} CH_2OH \\ CH_2OH \end{matrix}$$

tendency and increase in strength of the formaldehyde-treated proteins can not readily be explained on the basis of either of these reactions. The hypothesis that has received general acceptance at present is that the formaldehyde also can set up crosslinks by secondary condensation of the methylol groups with other reactive hydrogen atoms, similar to that which occurs in Mannich reaction (2). Evidences for the formation of crosslinks

$$-NHCH_2OH + HR \rightarrow -NHCH_2R + H_2O$$

have been obtained (3,4).

The amino group which reacts with formaldehyde is generally believed to be furnished by lysine residue (I) which appears to be held by peptide linkage in the protein molecule through the carboxyl and α-amino groups, the ε-amino groups thus left free is used in combining with formaldehyde. Reaction of the guanidyl



(I) (II) (III)

group of arginine (II) with formaldehyde has often been assumed. Some investigators believe that the reaction does occur at room temperature but only in alkaline media. Evidence has, however, been found by Fraenkel-Conrat and Olcott (4) that guanidyl group binds formaldehyde in neutral and acid solution of 70°. Histidine (III) is another basic amino acid which has been found

in protein molecules. It might conceivably react with formaldehyde. Other formations found in proteins that have been suggested by various investigators as being likely reactants with formaldehyde are amide, thiol, indole, disulfide and some basic, phenolic and aliphatic hydroxyl groups, as well as the polypeptide chain itself (5,6).

Elevated temperatures and acid reaction media have recently been found more useful for the formaldehyde-protein reaction. The amount of combined formaldehyde is increased and the physical properties of the reaction product - the strength of the protein fibers, for example - is greatly improved. These remarkable changes may partly be attributed to the denaturation of protein: With the internal collapse of the protein structure upon itself during denaturation, a change in dipolar ionic configuration might have occurred, resulting in the conversion of certain electrovalent salt linkages to coordinate ones. The structural breakdown might well bring into justa-position more of the weakly basic imino groups of adjacent polypeptide chains which, according to Theis, result in a further bridging and increased aldehyde fixation (7). Wormell and Kaye (8) and Fraenkel-Conrat,

$$>NH + HCHO + HN< \quad \rightarrow \quad >N-CH_2-N<$$

Cooper and Olcott (6) state, however, that secondary reaction occurs under the mentioned conditions largely by means of crosslinking on to the amide groups using the formaldehyde already attached to amino groups.

$$-NHCH_2OH + H_2NCO- \quad \rightarrow \quad -CONHCH_2NH- + H_2O$$

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Reported by T. L. Tan
May 15, 1946

REPLACEMENT REACTIONS AT AN ASYMMETRIC CARBON ATOM

The extensive work of Hughes, Ingold, and their coworkers on the mechanism of substitution reactions and on the Walden inversion and the work of Winstein, Lucas, and their coworkers on replacement reactions in the presence of neighboring groups make it possible to predict with some assurance the configuration to be expected when one substituent on an asymmetric carbon atom is replaced by another.

Let us first consider the two general mechanisms of the replacement reaction. The hydrolysis of methyl bromide in alkaline aqueous alcohol illustrates the S_N2 mechanism. Reaction occurs by approach of the reactant, hydroxyl ion, from the rear side of the methyl bromide. $CH_3Br + OH^- \rightarrow CH_3OH + Br^-$. As the hydroxyl ion approaches, the C-Br bond stretches until in the transition state both the hydroxyl group and the bromine are attached equally

firmly to the central carbon. Reaction is completed by loss of a bromine from this highly unstable transition molecule. Loss of hydroxyl also occurs, of course, and this constitutes reversion to unaltered starting materials (2 p. 131, 158; 3b).

S_N2 represents substitution, nucleophilic, bimolecular.

The hydrolysis of t-butyl bromide by aqueous alcohol illustrates the second type of mechanism, S_N1 (3a, 2 p. 166). In this mechanism the slow step consists of the ionization of the

$$(CH_3)_3CBr \rightleftarrows (CH_3)_3C\cdots Br(\text{solvated}) \rightleftarrows (CH_3)_3C^+(\text{solv.}) + Br^-$$

$$(CH_3)_3C^+\begin{matrix}(H_2O)_m\\(EtOH)_n\end{matrix} \rightarrow (CH_3)_3C\overset{+}{O}H_2 \rightarrow (CH_3)_3COH + \text{solv.} + H_3O^+$$

alkyl halide. This ionization is transient, lasting only the barest instant of time. Furthermore, the solvent participates actively in this dissociation, both ions being closely surrounded by solvent molecules (3a p. 988). Very rapidly after separation of the bromide ion from the carbon atom one of the molecules of the solvation layer collapses onto the carbon to give the t-butyl alcohol or ether. The C-Br bond has to be stretched only a fraction of an Å unit (3a, p. 985) before it has passed the critical distance involved in the transition state for the dissociation. This critical distance represents the balance point at which return of the bromine to the normal C-Br distance and complete separation are equally probable. Although solvent molecules are involved, their concentration does not change appreciably during the reaction, and it is convenient to consider the solvent as the background against which single

molecules of t-butyl bromide slowly ionize and then with which they rapidly react. S_N1 thus means substitution, nucleophilic, unimolecular.

If we consider the steric effects to be expected under these two different mechanisms, it is apparent that S_N2 should always cause an inversion, while the effect of S_N1 is not so certain *a priori*.

The proof that in several typical examples of the S_N2 reaction every reactive collision involves an inversion is as follows,

1. The rate of the exchange reaction $RI + I^{*-} \xrightarrow{\text{acetone}} RI^* + I^-$ was determined by the use of radioactive iodide or bromide ion with three halides, s-octyl iodide, α-phenylethyl bromide, and α-bromopropionic acid. The rate of the racemization of these halides by iodide or bromide ion was also determined. These rates were identical within the experimental error. If non-inverting exchanges occur, then the rate of exchange should be greater than the rate of racemization (2 p. 165).

2. The S_N2 hydrolysis and alcoholysis of s-octyl bromide (and of α-bromopropionic ester and acid) leads to products of inverted configuration with 95-100% inversion taking place during the substitution (1 pp. 1196-1236). See Table I.

The results with some typical S_N1 reactions are also given in Table I. It appears that an S_N1 mechanism leads to inversion together with more or less extensive racemization. The partial retention of configuration is not difficult to explain - it is merely necessary to postulate that the carbonium ion is so reactive that a solvent molecule from the solvation shell collapses onto it, a) before the separating bromine ion has time to get out of the way of solvent molecules that might drop in from the "front" side, and, b) before the ion has had time to oscillate into the opposite configuration.

According to this picture the more stable the ion R_3C^+, the more time it will have to become racemized by b or to give a racemic product by a. Thus α-phenylethyl chloride, whose ion tends to be stabilized by resonance is more extensively racemized during substitution than is s-octyl bromide.

Another cause for a longer "life" of the positive ion might be a decrease in the proportion of reactive molecules in the solvation shell. Thus racemization on hydrolysis should increase as water is replaced by acetone in the solvent. Reference to Table I shows that this prediction is fulfilled in the hydrolysis of α-phenylethyl chloride in water, 60% acetone, and 80% acetone.

Another factor must be considered in all of these reactions. Although each reactive collision in an S_N2 reaction leads to inversion, the product may turn out to be largely racemic due to

TABLE I

Effect of Substitution on Steric Configuration

Solvent	Concn.[a] of acid or base	S_N2 %	S_N1 %	Retention[b] of optical purity (%)
	Ethyl Alcoholysis of s-octyl bromide (1 p. 1200)			
Anhyd. EtOH	2.18-1.67 NaOEt	100	0	-100
60% EtOH (aq)	1.23-0.91 KOH	95	5	- 95
"	0.00-0.31 HBr	0	100	- 74
	Hydrolysis of s-octyl bromide (1 p. 1205)			
60% EtOH (aq)	1.23-0.91 KOH	88	12	- 93
"	0.00-0.31 HBr	0	100	- 66
	Calcd. for	100	0	- 96
	Hydrolysis of α-phenylethyl chloride			
Water (20°)	0.00-0.13 HCl	0	100	- 17.5
60% Acetone	0.00-0.04 HCl	0	100	- 5.4
80% Acetone	0.00-0.19 HCl	0	100	- 1.9
	Ethyl alcoholysis of α-phenylethyl chloride			
Anhyd. EtOH	2.85-2.7 NaOEt	92.5	7.5	-High
"	0.00-0.14 HCl	0	100	-Low

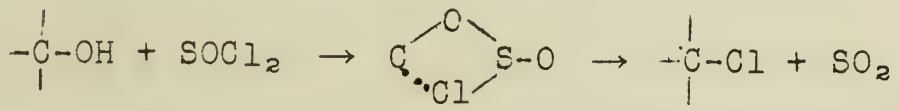
(a) HBr or HCl is formed in these reactions.
(b) The negative sign indicates inversion of configuration.

side reactions. One such side reaction is the bimolecular racemization of alkyl bromide by bromide ion which has already been mentioned. Another type of racemization takes place when α-bromopropionic ester is treated with sodium methoxide in methanol. Methoxyester was formed with only -2.7% retantion (see Table I) of activity. Investigation showed that this was due to racemization via the action of methoxide ion on the active α-hydrogen which was taking place about 35 times as fast as etherification (k_2 in min.$^{-1}$ g.-mol.$^{-1}$ for racemization 0.888, for etherification, 0.0252), and that when a correction was made for this racemization, the ether formation was found to take place with complete inversion as required by the S_N2 mechanism.

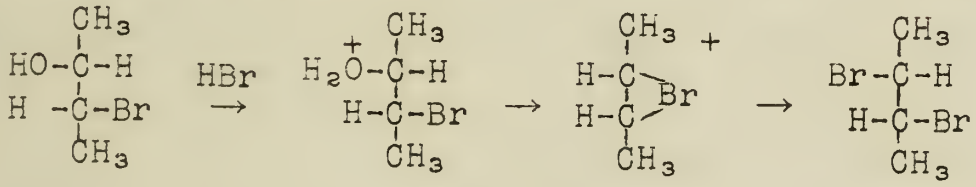
Thus far we have considered reactions which lead to inversions. In Table II are listed a few examples of substitution reactions which lead to retention of configuration. Hammett (2 p. 182) has pointed out that a sequence of two S_N2 reactions

should lead to retention of configuration, as for example $CH_3Br + I^- \rightarrow CH_3I + Br^- \xrightarrow{H_2O} CH_3OH$, which would lead to retention of configuration if it took place with an optically active halide. In the known examples in which configuration is retained, however, the formation of a cyclic intermediate is possible.

The formation of a cyclic intermediate in the reaction of carbinols with thionyl chloride has been proposed (1 p. 1267) to explain the reaction of compounds such as α-phenylethyl alcohol which give a chloride with retention of configuration. If pyridine is present, inversion occurs.

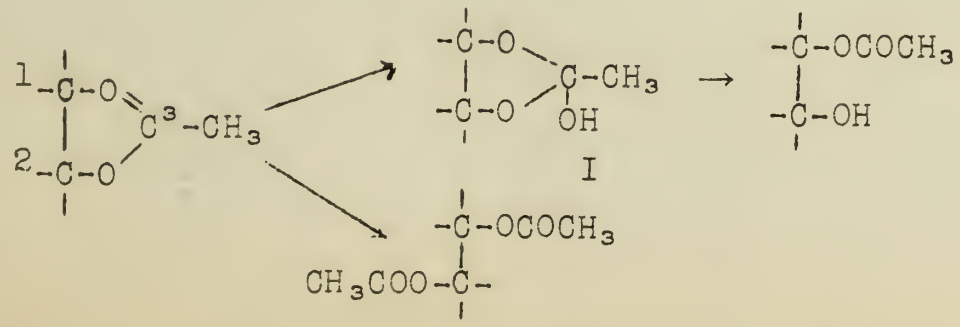


A second type of cyclic intermediate has been proposed for the reactions shown in Table II. Here the adjacent bromine, hydroxyl, methoxyl, or carboxylate group can form a three-membered ring (2 p. 148, 4a p. 2846). The formation of this ring also



serves to explain the established <u>trans</u> addition of bromine to double bonds such as the formation of <u>dl</u>-butylene bromide from <u>cis</u>-2-butene, Table IV. The intermediate with a neighboring hydroxyl is the conjugate acid of the corresponding epoxide, with the carboxylate it is one form of a betaine.

A third type of cyclic intermediate evidently is involved in certain reactions where an acetoxy group is adjacent to the reacting group. Some examples of these reactions are given in Table III. Although the reactions have not yet been completely worked out, it is possible with the aid of a bit of speculation to "explain" nearly all of them. Winstein proposes that the intermediate involved is the ion of an ortho ester which can then



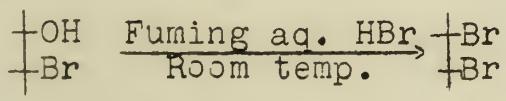
react farther either by attack at C-3 or by an S_N2 attack at C-1 or C-2. The first alternative will lead to inversion of configuration, the second, to retention. Water and alcohol lead to reaction at C-3, whereas potassium acetate reacts at C-1 and C-2.

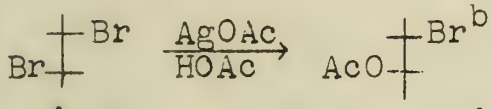
In support of this hypothesis Winstein has been able to isolate the orthoester (I with hydroxyl replaced by ethoxyl) from the reaction of trans-2-acetoxycyclohexyl p-toluenesulfonate with potassium acetate in absolute ethanol.

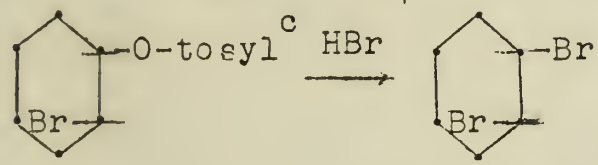
TABLE II

Reactions Involving Neighboring Groups[a]

Reactions involving Br

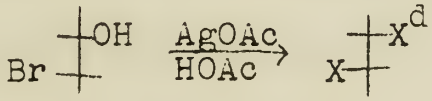
1 

2 

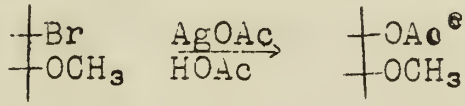
3 

4 cis-butene → dl-Dibromide

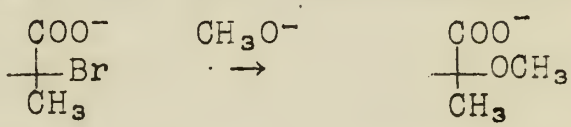
Reactions involving hydroxyl

5 

Reactions involving methoxyl

6 

Reactions involving carboxylate

7 

1 (4a p. 1576); 2 (4b p. 2780); 3 (4b p. 2792); 4 (Table IV); 5 (4b p. 2787); 6 (4b p. 2196); 7 (1 p. 1210).

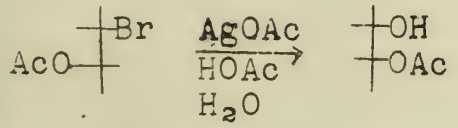
(a) The compounds represented are 2,3-substituted butanes written with the methyl groups at the top and the bottom in every case, and cyclohexane derivatives. In most examples dl mixtures were used although only one form is shown.
(b) Shown to be an intermediate (4b p. 2788).
(c) Tosyl = $p\text{-}CH_3C_6H_4SO_2$.
(d) Isolated as the diacetate.
(e) Isolated as the methoxy glycol.

TABLE III

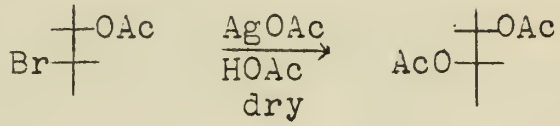
Reactions Involving a Neighboring Acetoxy Group

Reactions involving inversion

1 

2 

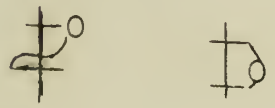
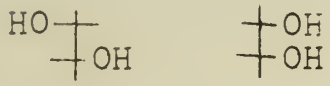
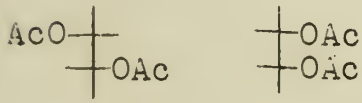
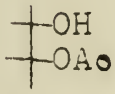
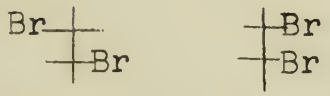
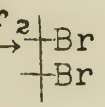
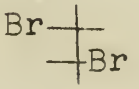
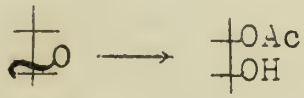
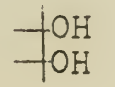
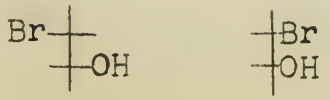
Reactions involving retention

3 

1 (4a 1581); 2 (4b 2787); 3 (4b 2780)
(a) Reactive intermediate which ordinarily undergoes further reaction to give the dibromide.

TABLE IV

Proof of Configuration of Products and Reactants

	Trans oxide has been obtained in optically active form (6, 4a 2845).
	dl in optically active form (6).
	From the glycol by Ac_2O (6). The reaction does not involve the asymmetric carbon (2 162).
	From the glycol (4a 1583, cf. Table I, p. 1582).
	dl in optically active form (4d 601) (4a 2786).
cis-butene trans-butene	Electron diffraction (7).
trans-butene $\xrightarrow{Br_2}$ 	Proof of trans addition from 5 and 6 (See also 8).
cis-butene → 	
	From 1 and 4 (4a 1583).
" 	From 1 and 2 (6); also cis oxide gives trans glycol.
	From butenes with H_2O + AcNHBr, from oxides + HBr. Trans addition is assumed by analogy with 7,8, and 9.

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(3) a. Bateman, Church, Hughes, Ingold, and Taher, J. Chem. Soc., 979 (1940).
b. Ref. 1, pp. 1253-1256.
(4) a. Winstein and Lucas, J. Am. Chem. Soc., 61, 1576, 1581, 2845 (1939).
b. Winstein and coworkers (Buckles, Hess, Henderson), ibid. 64, 2780, 2787, 2791, 2792, 2796 (1942); 65, 613, 2196 (1943).
c. Winstein and Grunwald, ibid. 68, 536 (1946).
d. Lucas and Gould, J. Am. Chem. Soc., 64, 601; 63, 2541 (1941).
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(6) Wilson and Lucas, J. Am. Chem. Soc., 58, 2396 (1936).
(7) Brockway and Cross, ibid., 58, 2407 (1936).
(8) Young, Dillon, and Lucas, ibid., 51, 2528 (1929).
(9) Kauffman, Organic Seminar Abstracts, April 28, 1943.
(10) Deasy, Organic Seminar Abstracts, Feb. 14, 1945.

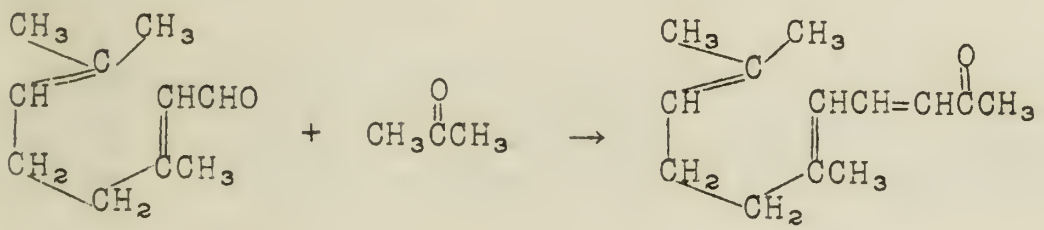
Reported by D. F. DeTar
May 15, 1946

IONONES

In search for a suitable synthesis of irone, a naturally-occurring compound thought to be responsible for the odor of violets, Tiemann, in 1893, prepared a new compound that was to be known as ionone. He was trying to prepare irone by the condensation of citral with acetone; however, the formula of citral accepted at that time was erroneous. Tiemann determined the true formula later.

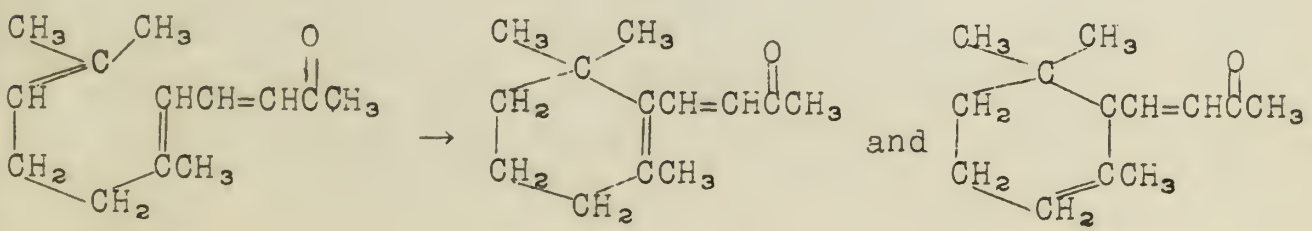
The discovery of ionone was an important development in the perfume industry because it provided a new group of compounds to be used as perfume bases. Ionone has been of more interest in late years in vitamin A research.

I. Preparation.--The most important method of preparing ionone is by the condensation of acetone with citral to form pseudoionone. Numerous modifications of the synthesis have been patented. An excess of acetone is usually desirable. Some of the reagents that have been used in the condensation are barium hydroxide, sodamide, alkali peroxides, sodium ethylate in absolute alcohol, and 10% caustic. Kenyon and Russel obtained a 45-49% yield using sodium in absolute alcohol. Ito got an 85-95% yield by using a 4-6% aqueous alkali solution.



Pseudoionone

The pseudoionone ring can be closed to form either α- or β-ionones by means of sulfuric acid. Concentrations of sulfuric acid above 75% yield mainly β-ionone while concentrations below 65% give a product containing more α-ionone. Phosphoric acid gives similar results. Other reagents used to close the ring are formic acid, aqueous ferric chloride, dilute nitric or chromic acid, phenol, and zinc chloride.



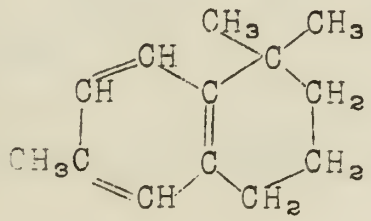
β-ionone α-ionone

II. Separation of α- and β-isomers.--Any commercial ionone is composed of a mixture of α- and β-ionones although one form may predominate. The first method of separation of the isomers was by formation of the semicarbazones. The beta derivative is more soluble in water than the alpha derivative. β-ionone can be steam distilled from a phthalic anhydride solution containing semicarbazones of both α- and β-ionone. A more complete separation was obtained by Young in 1944 by steam distillation of β-ionone from a sulfuric acid solution of the semicarbazones.

The bisulfite additon compound of β-ionone dissociates more readily than that of α-ionone; therefore, β-ionone will steam distill first. Another separation of the α- and β-bisulfite addition compounds is based on the insolubility of the alpha derivative in saturated sodium chloride solution.

III. Resolution of dl in α-ionone.--It can be seen from the formula of α-ionone that the carbon from which the side chain emanates is an asymmetric carbon. Optically active α-ionone should be useful as an indicator for the stability of the double bond system. Any conditions which would cause an equilibrium between α- and β-ionone would lead to racemization of the alpha form. In 1943, Sobotka resolved dl-α-ionone by the use of l-menthoxyhydrazide.

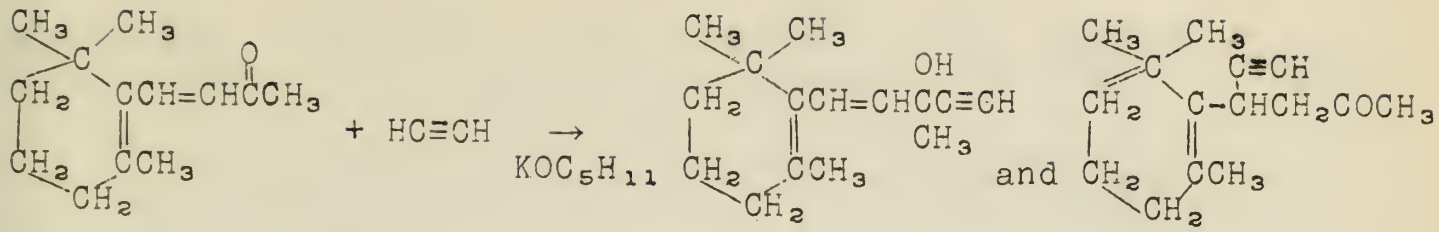
IV. Reactions of ionone.--If ionone is heated in the presence of hydrogen iodide and red phosphorus or iodine alone, ionene is formed. By oxidative degradations and by its synthesis from metaxylene, ionene was proved to be 1,1,6-trimethyltetralin.



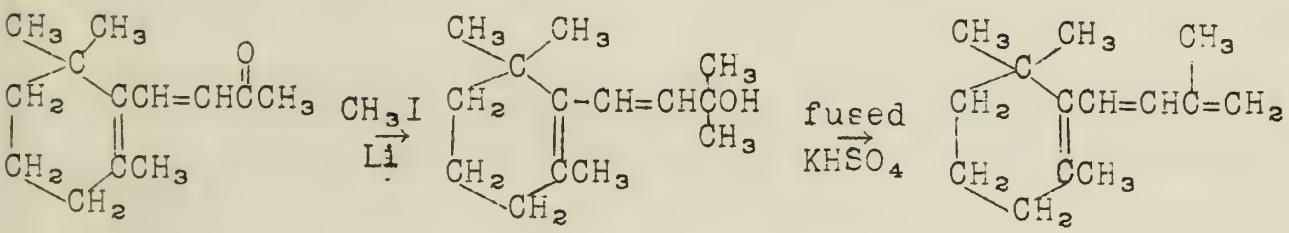
ionene

Using platinum as a hydrogenation catalyst, Skita in 1912 obtained dihydroionone and tetrahydroionone. In 1937, Kandel conducted a series of hydrogenations of ionones using a nickel catalyst. He found that the temperature determined the extent to which the hydrogenation took place. He also found the groups were reduced in the following order; (1) the olefin link in the side chain, (2) the carbonyl group, and (3) the olefin link in the ring. In complete reduction there was dehydration of the alcohol.

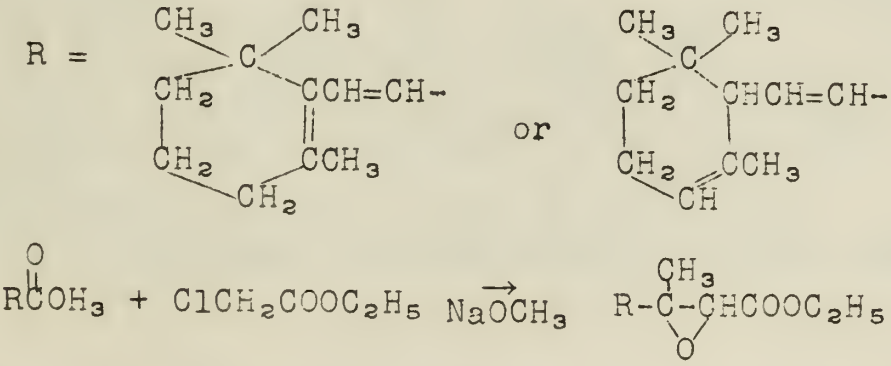
Acetylene will add to β-ionone giving equal amounts of the 1,2 and 1,4 additon products in yields of 80% if potassium t-amylate is used as a catalyst.



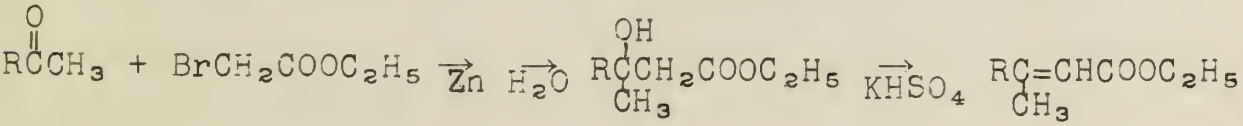
Kipping and Wild found that β-ionone would react with methyl iodide in the presence of lithium to form the expected alcohol. If the alcohol were dehydrated, a triene was obtained.



Heilbron in 1942 proposed a synthesis of vitamin A the first step of which consisted of the reaction of β-ionone with ethyl chloroacetate in the presence of sodium methoxide. He obtained the glycide ester of β-ionone in 60% yields and the glycide ester of α-ionone in 30% yields.

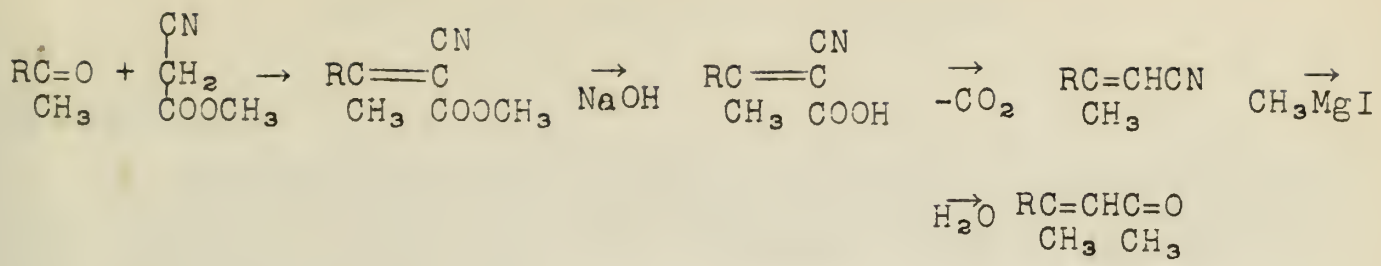


In 1943, Sobotka found that the dry distillation of barium ethyl ionylidene acetate prepared from either α- or β-ionone by a Reformatsky reaction led to α-ionone only. Sobotka favors the theory that isomerization takes place during the Reformatsky reaction and that there is no β-ionylidene acetate.



ionylidene acetate

Young has studied ionylidene acetate, ionylidene cyanoacetic acid, and similar compounds as a means of synthesizing compounds analogous to vitamin A. He has prepared ionylidene acetone in the following manner. Young's study of the absorption



spectra of α- and β-ionylidene acetates agreed with Sobotka's. On the following chemical evidence, Young favors the existence of both α- and β-ionylidene acetate. (1) On ozonolysis, he obtained isogeronic acid and geronic acid from α- and β-ionylidene acetates respectively. (2) He prepared α- and β-ionylidene acetones from ionylidene acetate obtained from α- and β-ionone.

After Young published his paper, Sobotka published an article defending his theory that only α-ionylidene acetate is formed by Reformatsky reaction on the basis of spectrographic evidence.

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Reported by Odette L. Shotwell
May 22, 1946

CONTROLLED ALKYLATION OF BENZENE

The Catalyst

1. Aluminum Chloride.--Aluminum chloride has been and still is the most generally effective and most convenient catalyst for the alkylation of benzene. The mechanism involved depends on the alkylating agent used.

2. Concentrated Sulfuric Acid.--Concentrated sulfuric acid is most effective as an alkylating catalyst when olefins and alcohols are used. Its reactions are characterized by high isomerization of the entering alkyl groups.

3. Phosphoric Acid and Phosphorous Pentoxide.--Phosphoric acid and phosphorous pentoxide require much more rigorous conditions when used as alkylating catalysts. Recently they have proved very effective for vapor phase ethylation of benzene.

4. Boron Trifluoride and Hydrogen Fluoride.--These catalysts require, generally, very mild conditions. They are very effective and alkylations go smoothly with an absence of tarry products and polymerizations.

The Control of Products

In the early work in which benzene was alkylated with halides and olefins in the presence of aluminum chloride various observations were noted. The reaction was reversible. The ease of alkylation increased with alkyl groups in the ring. Polyalkylated products appeared early in the reaction mixture. The number of groups entering the ring depended on the type of alkyl group. Methyl groups could replace six hydrogen atoms, whereas tert-butyl groups would only replace two hydrogen atoms. Isomerization of the alkyl groups entering generally occurred to a large extent. The meta position for two or three groups entering the ring was generally favored over the para or ortho.

The liquid phase alkylation of benzene using ethylene and aluminum chloride has been studied quite completely. In the early work the concentration of aluminum chloride was seen to have a marked effect on the products.

Reid and coworkers have made the most thorough study of the ethylation of benzene. They have clarified enormously the general course of the reaction, studying the general distribution of ethylene in the ethyl benzenes obtained, the effect of the benzene-aluminum chloride ratio, the effect of temperature, and the effect of water.

Their results from the most recent studies are recorded in Tables I and II. In these experiments the ethylene was led in at 268 cc/minute. In Table II three moles of ethylene were added.

The conclusions reached from these studies are as follows. An increase in the concentration of aluminum chloride over the benzene concentration increases the yield of triethyl benzene. The triethyl benzene occurs in the highest percentage of alkylated products when three moles of ethylene are added. Increasing the amount of ethylene added leads to the formation of the hexa-ethyl benzene in high yields. Water in very small quantities accelerates the preliminary absorbtion of ethylene.

With the increased demand for large quantities of styrene, the vapor phase ethylation of benzene has become important. Aluminum chloride--sodium chloride--pumice and phosphoric acid--kieselguhr have been found to be highly effective for the continuous flow, vapor phase ethylation of benzene at high pressures and temperatures. At a pressure of 6000 lbs/square inch and temperatures of 200-320°C using the phosphoric acid-kieselguhr catalyst, over 80% of the ethylene and benzene was converted into ethyl benzene, and by the proper control of ethylene and benzene used, over 90% of the ethyl benzenes was mono-ethyl benzene.

TABLE I

Moles of Ethylene	% Distribution of Ethylene					
	Mono	Di	Tri	Tet	Penta	Hexa
1	27	24	12	8	11	18
2	9	45	28	13	2	3
3	0.3	9	56	25	4	6
4		1	17	32	27	18
5				11	39	50

TABLE II

$C_6H_6/AlCl_3$	% Distribution of Ethylene					
	Mono	Di	Tri	Tetra	Penta	Hexa
4	0.1	5	60	30	1	4
18	0.2	9	52	29	4	6
20	0.4	10	51	27	6	5
23	0.4	17	45	28	12	5

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Reported by Paul E. Hoch
May 22, 1946

HYPERCONJUGATION

In recent years an attempt has been made to extend our knowledge of the properties of organic molecules so that reactions may be explained and eventually predicted by a logical concept of electron displacements and mobilities. In the development of this concept two general effects have been recognized. The first of these, the general inductive displacement (I), is the unequal sharing of an electron pair by two atoms, yet so that the electron pair remains within the valence shell of each atom. Thus in methyl chloride the electron pair constituting the carbon-chlorine bond is held somewhat more tightly by the chlorine atom than by the carbon atom. The static inductive effect (I_s), or simply the

$$\overset{\delta+}{H_3C} \quad \overset{\delta-}{:Cl}$$

"inductive" effect, is a permanent displacement characteristic of the molecule. The dynamic inductive, or inductomeric, effect (I_d), is a temporary enhancement of the I_s effect by the environment of the molecule.

The second general effect, the tautomeric displacement (T), is associated with multiple covalent bonds or unshared electron pairs. The first case is characterized by the tendency of one atom to withdraw an electron pair from the multiple link and in the second an electron pair is released toward the adjacent atom so that the covalence of the link tends to increase. The permanent

$$R_2\ddot{N}-CH=CH-CH=\ddot{O} \rightleftarrows R_2\overset{+}{N}=CH-CH=CH-\overset{-}{O}$$

state of tautomeric displacement is designated the mesomeric effect (M), while the temporary enhancement brought about by the environment is called the electromeric effect (E).

Studies of various reactions, such as the unimolecular hydrolysis of alkyl halides, have indicated that the inductive effect (I_s) of alkyl groups diminishes in the order t-Bu > i-Pr > Et > Me. However, certain other reactions, such as the unimolecular hydrolysis of p-alkyl substituted benzyl halides, give either partial or complete inversion of this sequence for degree of electron release. An attempt to explain this inversion has led to the development of the theory of hyperconjugation. Baker and Nathan proposed that the duplet of electrons forming a carbon-hydrogen bond of an alkyl group which is attached to an unsaturated carbon atom is less localized than that in a carbon-carbon bond; hence, electron release is permitted by a tautomeric mechanism.

$$H-CH_2-C=C-$$

This effect would act in additon to andin the same direction as the inductive effect, but would be expected to decrease in the order Me > Et > i-Pr > t-Bu.

There are certain data in the field of physical-organic chemistry which may be interpreted in such a manner as to lend support to the theory of hyperconjugation. Pauling and coworkers have shown from electron diffraction studies of methylacetylene and similar compounds that the length of the carbon-carbon single bond adjacent to the carbon-carbon triple bond is approximately 0.08 Å less than the normal carbon-carbon single bond length of 1.54 Å. This shortening of the length of the single bond was attributed to a partial double-bond character due to hyperconjugation effects which are illustrated by the formulas below.

$$H^+\ CH_2{=}C{=}\ddot{\bar{C}}H \qquad\qquad H{\cdot}CH_2{=}\dot{C}{=}CH$$

Hurdis and Smith have assumed certain dipole moment phenomena to be caused by hyperconjugation. The large increase in dipole moment of methylchloroform over that of chloroform was considered to be evidence for the occurrence of structures of the following type.

$$H^+CH_2{=}CCl_2\bar{C}l$$

Work by Mulliken on molecular refractivities, absorption spectra and heats of hydrogenation of conjugated dienes, as well as Baker, Dippy, and Page's determination of the dissociation constants of p-alkyl substituted benzoic acids support the concept of hyperconjugation.

Further evidence in favor of hyperconjugation has been obtained from a study of reaction kinetics. Baker and Nathan have studied the kinetics of the bimolecular reaction between para-substituted benzyl halides and pyridine. The reaction should be facilitated by an accession of electrons to the side chain, thus enhancing the separation of the halogen as the halide ion. A substituent in the para position should affect the rate according to the degree with which it could donate or withdraw electrons to or from the benzene ring. It was found that alkyl groups increased the rate of reaction in the following order: Me > Et > i-Pr > t-Bu.

Hughes, Ingold, and Taher have presented the first unequivocal data in support of hyperconjugation. Their criticism of Baker and Nathan's work is especially valuable in that it can be applied to practically all studies of reaction kinetics. Whether studying reaction rates or equilibria four influencing factors must be taken into consideration; the general inductive and the tautomeric effects on both initial and transition states for reaction rates, and on both initial and final states for equilibria. Only by making one of these four effects much greater than the other three can the special consequences of that one effect be studied accurately. Furthermore, there must be a well-spaced, regular, and complete sequence of rate or equilibrium constants, backed by corresponding and analogously regular activation or reaction heats.

To fulfil these requirements Hughes, Ingold, and Taher studied the reaction rate of the unimolecular hydrolysis of p-alkyl substituted benzyl chlorides. In such a system the transition state is the determinative state. Furthermore the tautomeric electron displacement, for which the system provides a mechanism, will be dominating, because the large electron demand created in ionization is not compensated by an electron transfer from a reagent, as in a bimolecular reaction. Rates and activation energies were obtained in a complete series, in the order Me > Et > i-Pr > t-Bu > H. The ratio of the rate constant for Me:H was 30:1, compared to the ratio of 1.65:1 obtained by Baker and Nathan.

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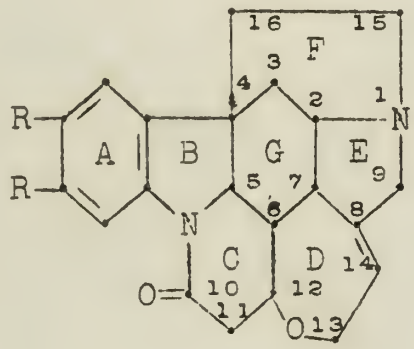
Reported by J. H. Saunders
May 29, 1946

STRYCHNOS ALKALOIDS

Nux Vomica seeds and Ignatius beans on extraction give a yield of two to three per cent of strychnos alkaloids. The two most important alkaloids of this group, strychnine and brucine, constitute almost the entire yield. In addition, small amounts of vomicine, strychnicine, struxine, α- and β-colubrine, and pseudo-strychnine are obtained. The modern chemistry of the strychnos alkaloids has thus far been mainly the chemistry of strychnine, brucine, and vomicine; the work in this field has been done almost entirely by the research groups headed by Leuchs, Robinson and Wieland. From their work a fairly clear picture can be obtained of the structure of strychnine and the relationship of strychnine to brucine, vomicine, and pseudo-strychnine.

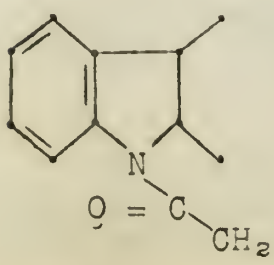


I, R = H. strychnine

II, R = OCH_3. brucine

A molecular structure for strychnine must take into account that (a) the empirical formula is $C_{21}H_{22}O_2N_2$; (b) strychnine is a mono-acidic, tertiary base having neither an N- or O- methyl group; (c) there is present one carbon to carbon double bond; (d) one of the two oxygens is present as a cyclic ether linkage and the other is present in a lactam group. The Robinson formula for strychnine, I, which embodies these characteristics, is now generally accepted as being correct in its main features. As a convenient means of summarizing the evidence for the Robinson formula, the structure will be divided into three fragments, a, b and c. In this way the controversy which still exists over fragment c can be considered separately.

The evidence for fragment a is summarized in the following statements.



fragment a.

1. The ultra violet absorption spectra for N-acetylcarbazole is very similar to that of strychnine.

2. Oxidation of strychnine with permanganate in alkaline solution yields N-oxalylanthranilic acid. (Brucine yields N-oxalyl-4,5-dimethoxyanthranilic acid.)

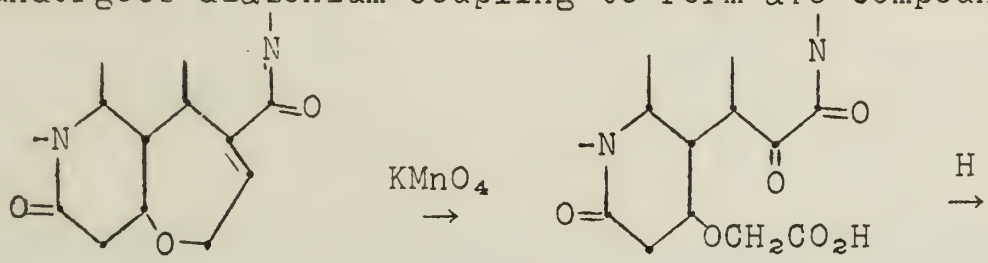
3. Nitric acid oxidation yields dinitrostrycholcarboxylic acid, which can be degraded by the Curtius method to dinitroisatin.

4. Distillation of strychnine from alkali yields both carbazole and tryptamine.

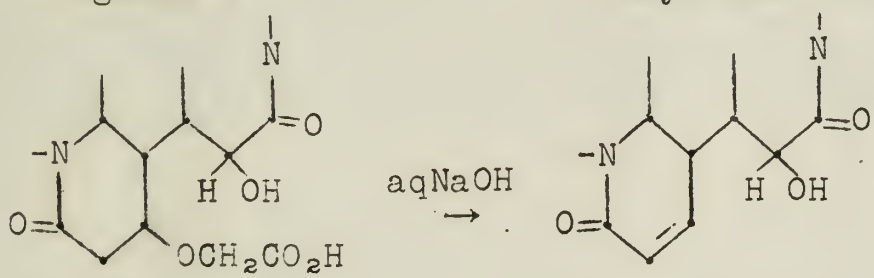
5. Strychnine reacts with benzaldehyde to form a benzylidine derivative (presumably at C_{11}).

6. Hydrolysis of strychnine yields an amino-acid, strychnic acid.

7. Electrolytic reduction of strychnine gives a di-acidic base, strychnidine, which has two tertiary nitrogen atoms. Strychnidine undergoes diazonium coupling to form azo compounds.

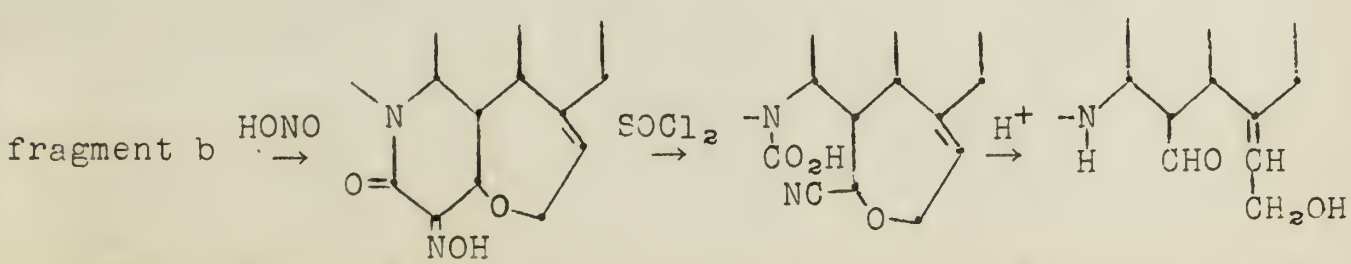


fragment b strychninonic acid



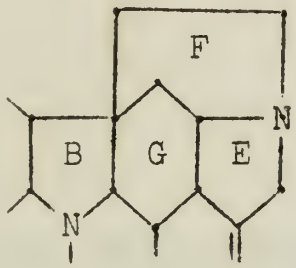
strychninolic acid strychninolone a + $HOCH_2CO_2H$

The evidence for fragment b lies mainly in the oxidative degradation reactions shown above. The formation of glycolic acid indicates the relationship between the carbon to carbon double bond and the ether linkage. Likewise the ready elimination of the glycolic acid group is strong support for the assumption that the ether linkage was beta to the amide group. Additional support for the structure of fragment b comes from an interesting Beckmann rearrangement of isonitrosostrychnine carried out by Wieland. This is shown below.

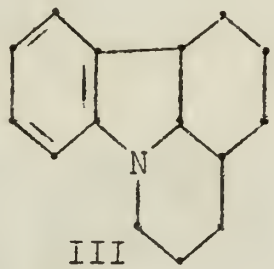


The evidence for the rest of the molecule, fragment c, is not very definite. Fusion of strychnine, strychninolone a, or strychninonic acid with KOH gives in each case β-indolylethylamine

(trytamine). This, in conjunction with the isolation of carbazole from the zinc dust distillation of strychnine, is the basis for postulating rings E and G. The remaining ring F is postulated to account for the fact that strychnine does not readily undergo dehydrogenation which a dihydroindole would be expected to do. Thus Robinson has prepared III and shown that it dehydrogenates easily to give the corresponding indole derivative.

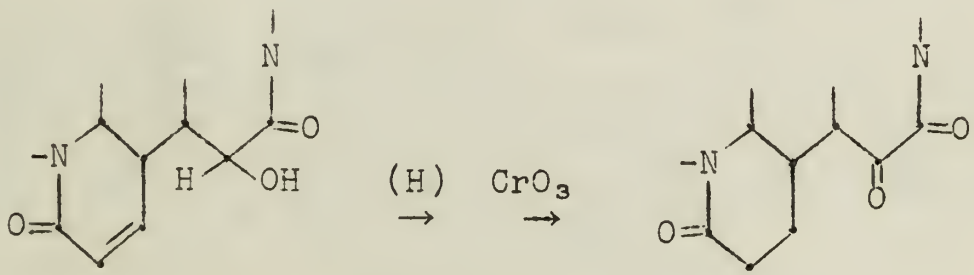


fragment c

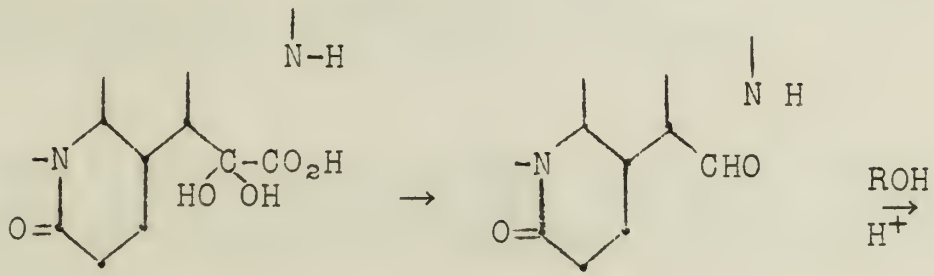


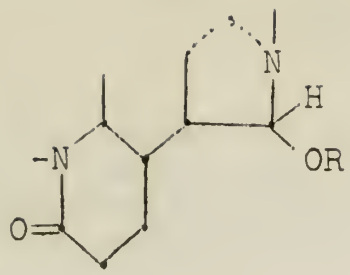
III

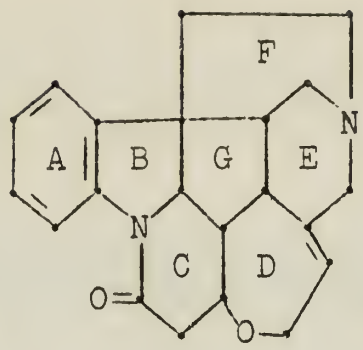
That the structure of fragment c of strychnine may very well be altered in the future is indicated by recent studies of Prelog. This work, which is summarized below, strongly indicates that ring E can readily lose one carbon atom to form a smaller ring. This would be expected for a six-membered ring but not for a five-membered ring. Prelog, therefore, writes the formula for strychnine as shown below.



strychninolone a







strychnine
(Prelog)

Work on the other alkaloids has resulted in a fairly clear picture of their relationship to strychnine. Brucine has been shown by several studies to be an o-dimethoxystrychnine as shown in formula II. Likewise pseudostrychnine has been fairly well demonstrated to be 9-hydroxystrychnine. Vomicine has two more oxygens than strychnine. One of these is present as an ether linkage between C_{10} and the aromatic ring; the other oxygen is probably present as an ether linkage in ring F.

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*The earlier references to the work of Leuchs, Robinson, and Wieland have all been indexed under the titles of strychnine, brucine, or strychnos and can therefore be readily found in the literature.

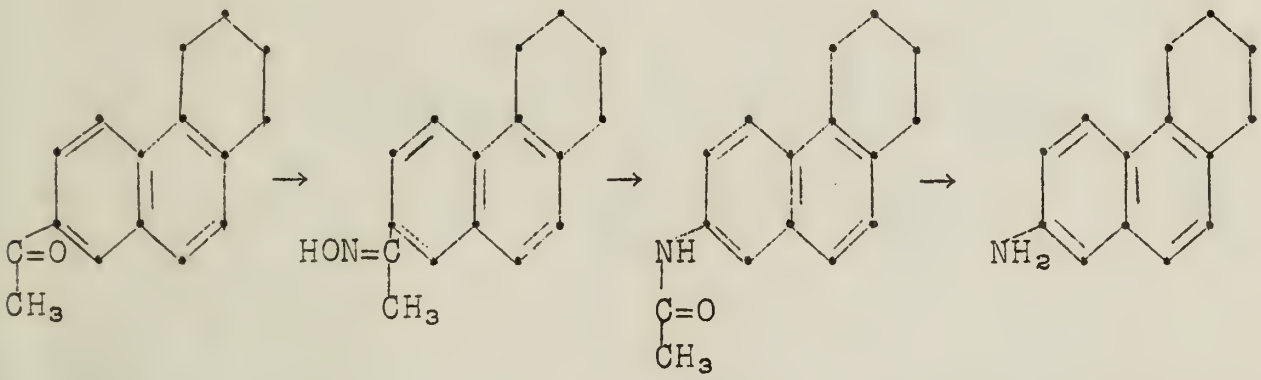
Reported by V. Boekelheide
May 29, 1946

THE SYNTHESIS OF COMPOUNDS RELATED
TO TETRAHYDROPHENANTHRENE*

In the search for compounds which would possess antimalarial activity, attention was directed to derivatives of 1,2,3,4-tetrahydrophenanthrene. The methods developed for the synthesis of some of the intermediates to the final drugs prepared are presented here.

7-Methoxy-8-acetyl-1,2,3,4-tetrahydrophenanthrene and 7-Methoxy-9-acetyl-1,2,3,4-tetrahydrophenanthrene. Griffing and Elderfield.--It was thought that 7-methoxytetrahydrophenanthrene could be obtained by conversion of the 7-amino or 7-sulfonic acid derivatives of the hydrocarbon. Both approaches were investigated.

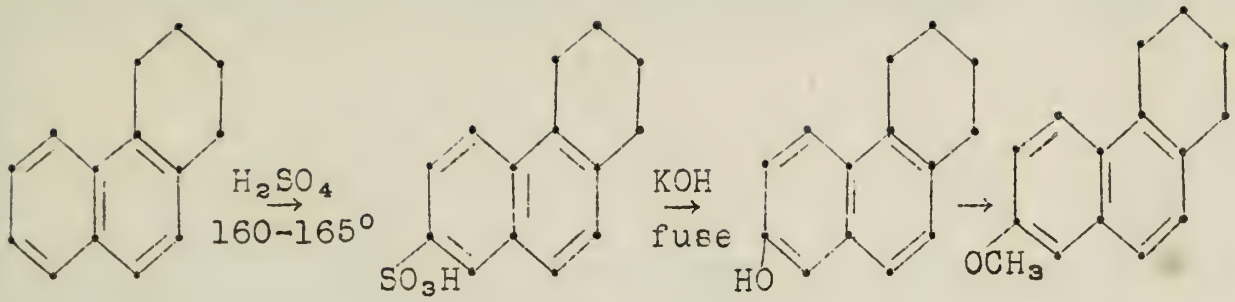
(a) From 7-aminotetrahydrophenanthrene.--Bachmann and Cronyn had prepared the 7-amino compound from 7-acetyltetrahydrophenanthrene through the oxime of this, Beckmann rearrangement to the acetylamino derivative and then hydrolysis, This involved an



initial separation of the 7- and 9-acetyltetrahydrophenanthrenes as obtained from the Friedel-Crafts reaction on the hydrocarbon in a ratio of 1:2. The yields from the fractional crystallization were considered too low to be practical.

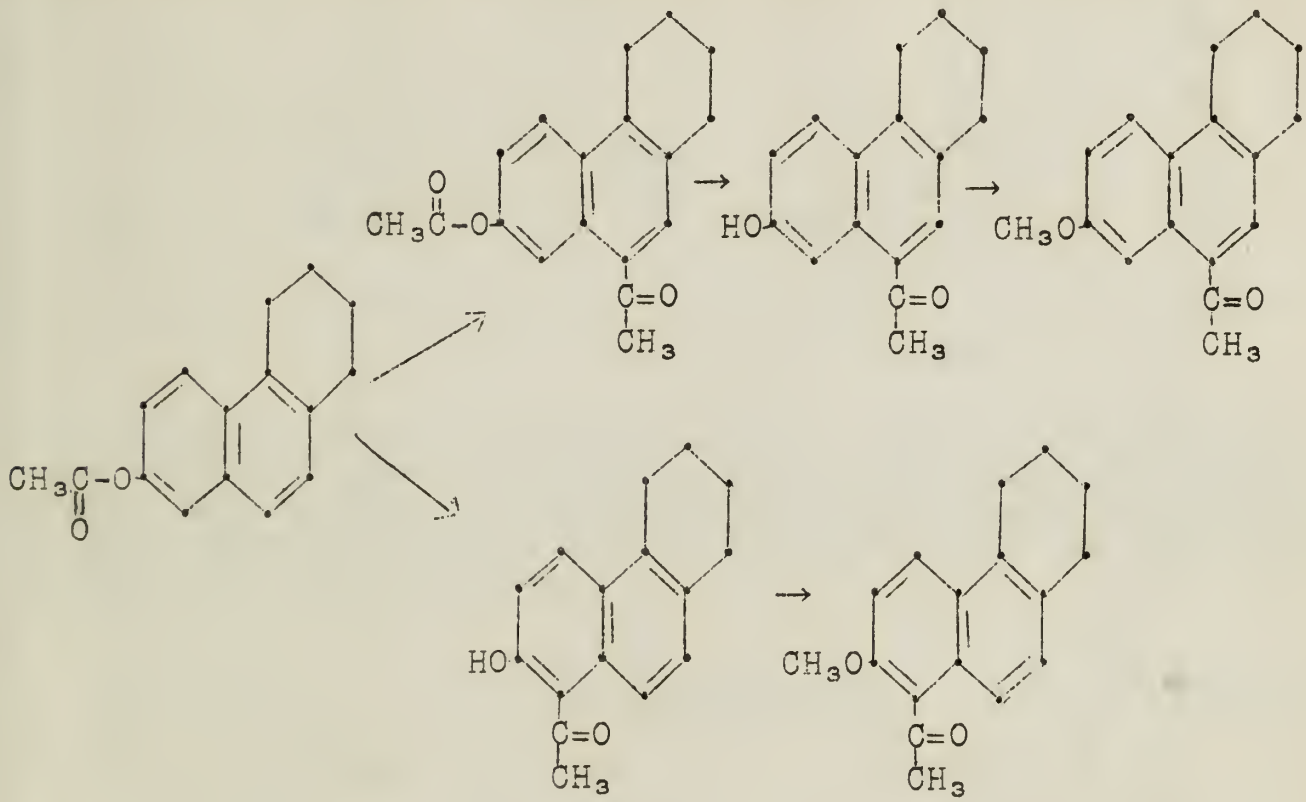
(b) From the 7-sulfonic acid.--There was no previous reference to direct sulfonation of tetrahydrophenanthrene but it was reasoned that it should behave as a 1,2-dialkylnaphthalene. Thus a reaction temperature of 160° would yield the 6, 7, or 10 sulfonic acid and at 80° the 5, 8, or 9 acid would be expected. While all attempts to sulfonate at the lower temperature failed, substitution at 160-165° afforded a 50% yield of the desired 7-sulfonic acid from which the 7-methoxy compound was prepared.

*This work was done under contracts, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the institutions with which the authors cited were associated.



(50%) (85-93%) (84%)

The preparation of the two acetyl derivatives was first attempted by direct acetylation. Again the problem of separating the 7- and 9-isomers by fractional crystallization caused a new method to be sought. The one which proved successful was as follows.

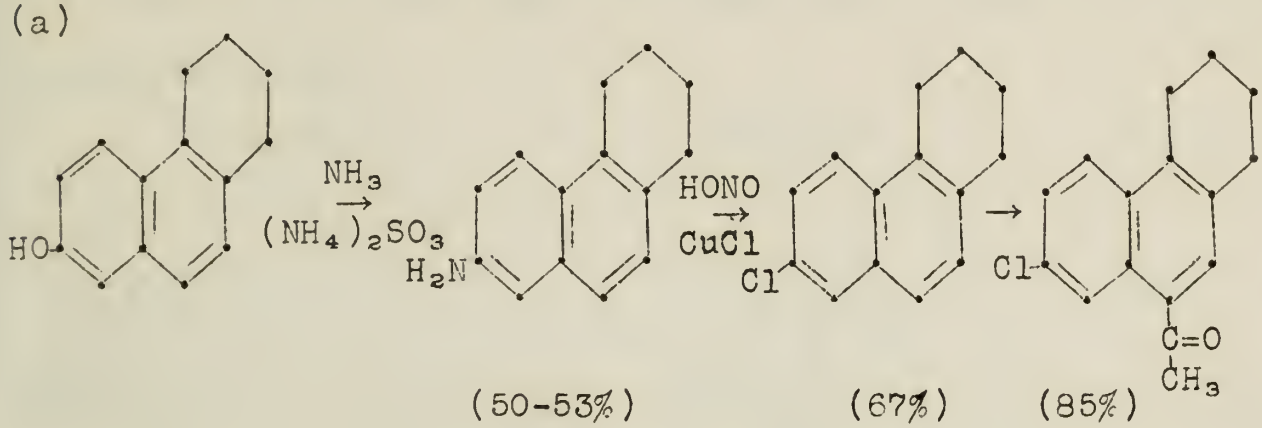


(60%) (80%)

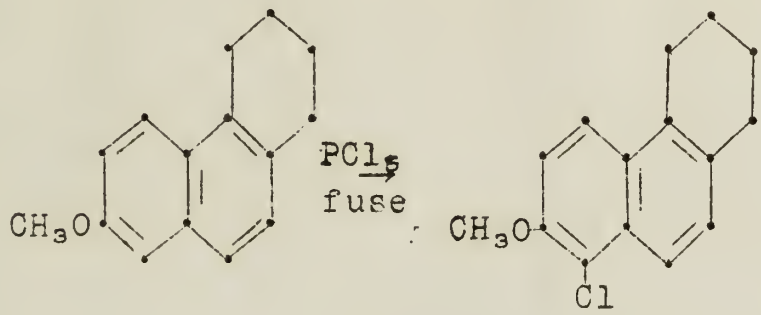
The structure of 7-methoxy-8-acetyltetrahydrophenanthrene was established by conversion to the known 1-ethyl-2-methoxyphenanthrene. The proof of structure for the 7-methoxy-9-acetyl compound will be published in a future paper.

<u>7-Chloro-9-acetyl-1,2,3,4-tetrahydrophenanthrene and 7-Methoxy-8-chloro-1,2,3,4-tetrahydrophenanthrene</u>. Kupchan and Elderfield.--

(a)

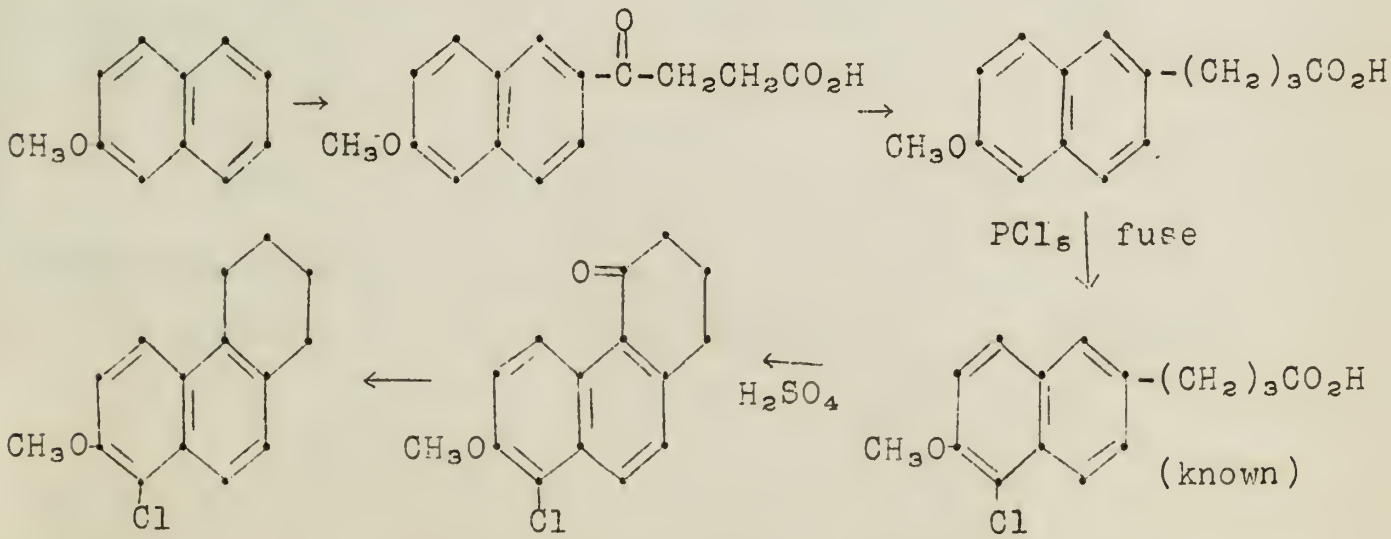


(b)



(80%)

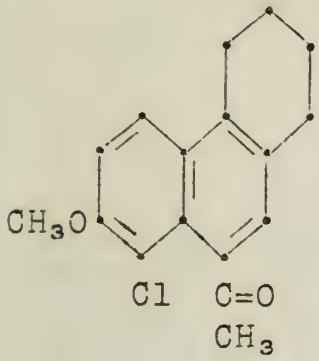
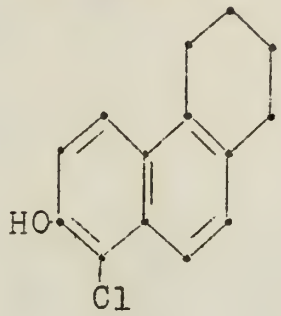
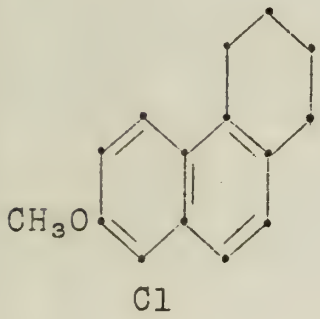
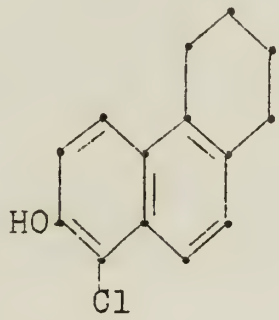
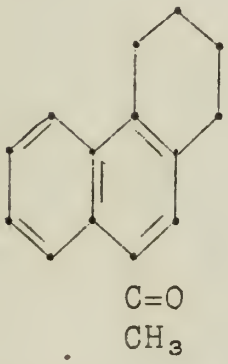
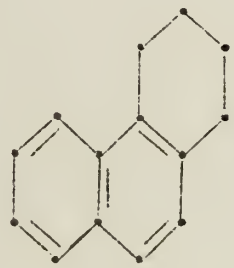
The structure of the 7-chloro-9-acetyl compound was proved by reduction of the acetyl and dehalogenation with palladium and hydrogen to give the known 9-ethyltetrahydrophenanthrene. Synthesis of the 7-methoxy-8-chloro derivative from β-naphthol methyl ether established its structure.



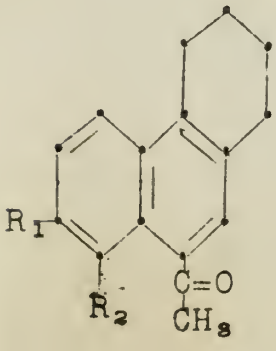
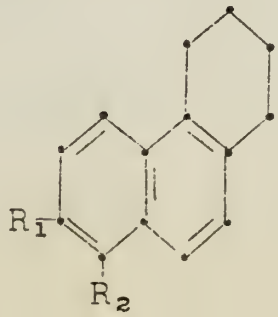
When the 7-methoxy-8-chlorotetrahydrophenanthrene was acetylated to give the 9-acetyl derivative and this treated with HBr to

demethylate the ether, it was discovered that ketone cleavage had also taken place and the acetyl group lost. This unexpected occurance led to a further investigation, the results of which are summarized below. Thus HI brings about reductive dehalogenation

Reaction with HBr

Compound	Product	Yield
		65%
		60%
		66%

Reaction with HI

Compound	Product	Yield
		

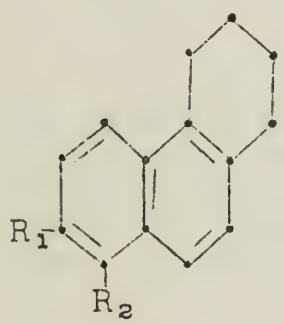
Reaction with HI (cont'd)

Compound	Product	Yield
R_1 - OCH_3 R_2 - Cl	R_1 - OH R_2 - H	75%
R_1 - OCH_3 R_2 - H	R_1 - OH R_2 - H	90%
R_1 - H R_2 - H	R_1 - H R_2 - H	66%

whereas HBr does not. In both cases the acetyl group was lost irrespective of the presence of substituent groups in the 7 or 8 positions. Reduction of the acetyl to an ethyl group and treatment with HBr or HI showed no loss of the ethyl in the product. Although Hill and Short in their study of hydrolytic fission with HBr of aromatic ketones in the desoxybenzoin series concluded that an hydroxyl or methoxyl group on the ring was necessary, apparently in this case the 9 position has a sufficiently high electron density without further activation to have cleavage occur.

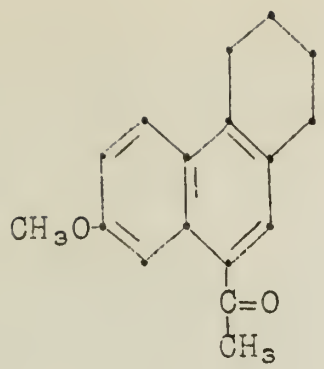
There also is a pronounced steric effect by a group in the 7-position on the 8-position and by a group in the 8-position on the 9-position. This is clearly shown by the following table.

(a)

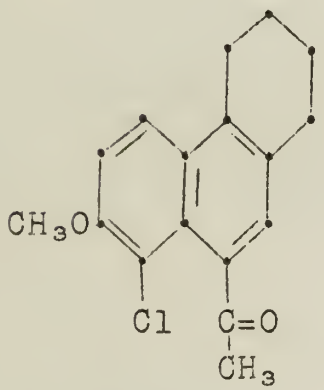


R_1 - OCH_3 R_2 - CHO	oxidation	no change
R_1 - OCH_3 R_2 - CN	hydrolysis	no change
R_1 - OCH_3 R_2 - $COCH_3$	oxidation	no change
R_1 - OCH_3 R_2 - Cl	H_2; Pd on $CaCO_3$	no change
R_1 - H R_2 - Cl	H_2; Pd on $CaCO_3$	R_1 - H R_2 - H (good yield)

(b)



1. Forms oxime readily.
2. Oxidizes to carboxylic acid in good yield.



1. Does not form oxime.
2. Will not oxidize to acid.

Robinson and Willenz have found the same behavior as in (a) on a similar compound.

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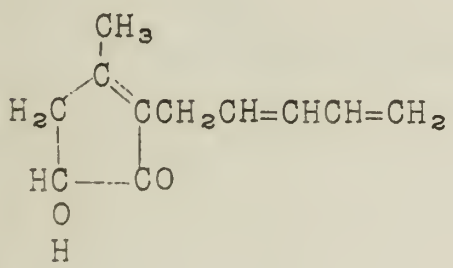
Hill and Short, J. Chem. Soc., 1123 (1935).
Robinson and Willenz, J. Chem. Soc., 393 (1941).

Reported by A. G. Anderson, Jr.
June 5, 1946

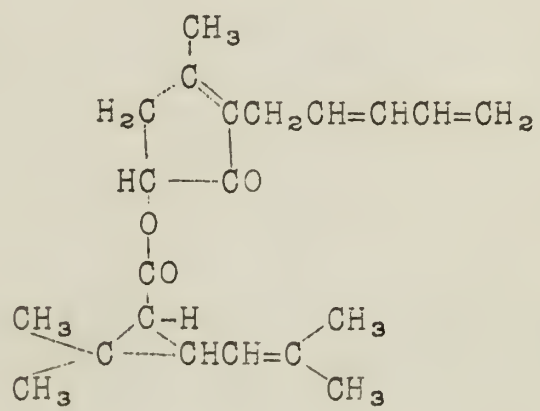
THE STRUCTURE OF PYRETHROLONE

Pyrethrolone (I) is the ketonic alcohol obtained upon hydrolysis of either pyrethrin I (II) or pyrethrin II (III). The structures of the pyrethrins have been discussed in a previous seminar, but since that time (1941) considerable work has been done toward more certainly determining the structure of pyrethrolone.

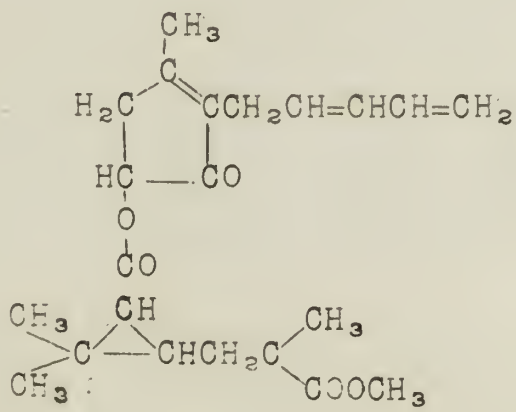
The pyrethrins are important constituents of most commercial fly sprays, since they give an immediate "knock-down" not exhibited by any other chemical compounds except the butyl cellosolve isocyanates which can be used to replace the pyrethrins as "knock-down" agents. The pyrethrins are obtained commercially from the dried flowers of Chrysanthemum cinerariaefolium, Vis. The flowers were first exported from Dalmatia about 1820, but the Japanese became the main producers during World War I and maintained this position until 1939 when the Kenya industry became the main supplier, probably because the pyrethrin content of the African flowers averaged 1.3% in comparison with 0.9% for the Japanese flowers.



I



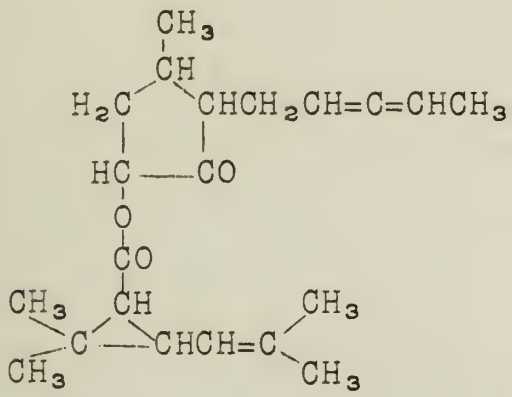
II



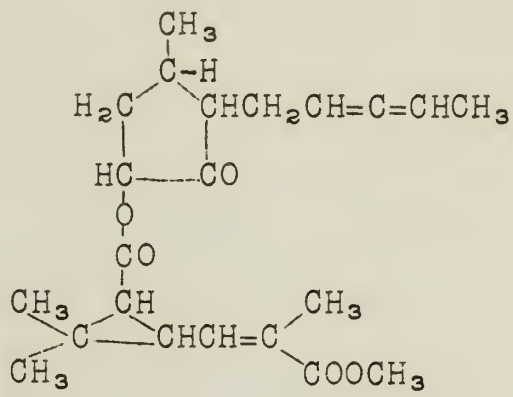
III

Unsuccessful attempts were made to determine the active constituent of pyrethrum flowers during the period 1854 to 1924, at which time Staudinger and Ruzicka published the results of six years of research on the problem. Their work has been called

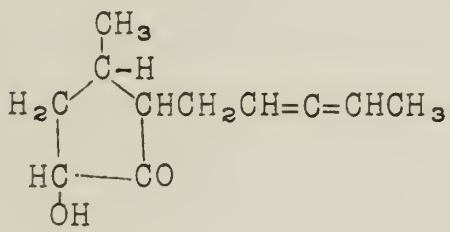
"one of the finest investigations in the history of plant-chemistry." They postulated the structures of pyrethrin I and pyrethrin II as formulas IV and V, respectively, and pyrethrolone as formula VI.



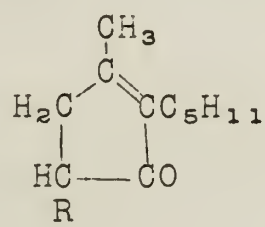
IV



V



VI



VII

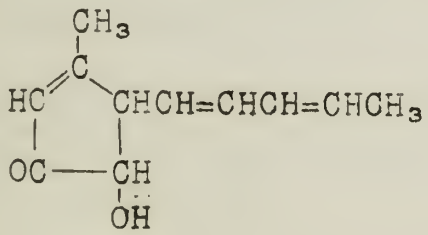
The structure of the pentadienyl side chain depended upon (1) the production of acetaldehyde on ozonolysis, (2) the isolation of malonic acid as a product after treating ozonolysis products with hydrogen peroxide, (3) the formation of acetic acid either by oxidation of pyrethrolone with permanganate or, together with acetaldehyde, on treating pyrethrolone mono-ozonide with water. Later, in a discussion of the constitution of jasmone, Ruzicka and Pfeiffer referred to the side chain of pyrethrolone and suggested that the allene double bond system (otherwise unknown in naturally occurring products) should be replaced by the more frequently-occurring conjugated dienoid system. This suggestion was made as a result of no further experimental work, but the position of the double bonds was held to be still much in doubt.

Subsequently it was shown by LaForge and Haller that tetrahydropyrethrone (VII, R=H) was identical with dihydrojasmone of known structure (VII, R=H). Tetrahydropyrethrone was obtained by hydrogenation of the side chain, giving tetrahydropyrethrolone (VII, R=OH). This compound was then chlorinated (VII, R=Cl), and reduced to tetrahydropyrethrone. Therefore they replaced the cyclopentanolone nucleus of Staudinger and Ruzicka with the cyclopentenolone structure. Thus, with the cyclopentenone nucleus and the proposed $^{*}CH=CH-CH=CHCH_3$ side chain, a trienone system was involved in pyrethrolone.

Comparison of the behavior of pyrethrolone and pyrethrone with allenes of known structure provided indirect evidence for the presence of the cumulated double bond system in the side chain. The isolation of acetaldehyde on ozonization was considered to be proof of the location of one of the double bonds in position 3, and to confirm the presence of a terminal methyl group. Thus with one double bond definitely located at position 3, the absence of the other one in position 1 would be positive evidence of the existence of the cumulated arrangement, since only position 2 would then remain. Therefore, when one mole of bromine readily added to pyrethrolone and pyrethrone, and the dibromo derivatives were reconverted into the original compounds by zinc reduction, LaForge and Acree found that 1-4 addition had not taken place, furnishing evidence of the presence of the cumulated system.

Studies of the absorption spectra of pyrethrolone, tetrahydropyrethrolone and pyrethrone and their derivatives by Gillam and West showed that the α,β-unsaturated ketonic grouping and a conjugated diene were both present as separately absorbing entities thereby eliminating the trienone system and the originally proposed cumulated system (VI).

They believed, however, that a terminal methyl group was present (indicated by formation of acetaldehyde on ozonolysis) which ruled out a side chain of structure I. On that basis they postulated structure VIII for pyrethrolone.



VIII

The conflict between the chemical and absorption spectra data led LaForge and Barthel to make a further investigation. It was pointed out that though structure VIII would account for the formation of acetaldehyde, it would not provide for the formation of malonic acid on oxidation. It became apparent that certain observations concerning pyrethrolone, hitherto considered unimportant, might have some bearing on the problem. Its distillation point was not constant, and its distillate always exhibited striations which indicated lack of homogeneity. The yield of acetaldehyde or ozonization did not exceed 30% of the theory, and a considerable quantity of formaldehyde was always formed. The values obtained on analysis of pyrethrolone and its derivatives were usually slightly high for hydrogen and low for carbon, as calculated for compounds with a double unsaturated side chain. The same observations were made in the case of pyrethrone. These facts were an indication that pyrethrolone was a mixture of compounds. This assumption was borne out by the results obtained by determinations of the carbon-linked methyl groups in fractions of pyrethrolone and its derivatives. The fractions obtained from pyrethrolone gave terminal methyl values decreasing with increase in boiling range and refractive index. The same was true for the fractions of its derivatives. It was presumed that the fraction with the highest

refractive index and boiling range would contain the largest proportion of the conjugated components of structure I, while the fraction with the lowest boiling range and refractive index would contain the largest component or components differing from (I) in having a side chain with the grouping $-C=CH-CH_3$.

Subsequently, five pyrethrolone semicarbazones were isolated from pyrethrin semicarbazone. Although the constituents with the higher terminal methyl content tended to accumulate in the earlier fractions, only incomplete separation could be accomplished owing to small differences in boiling range. The tendency of pyrethrolone to polymerize on protracted heating was another difficulty. Nevertheless, a fraction could be isolated in small quantity which contained but one equivalent of terminal methyl. This fraction consisted almost entirely of pyrethrolone corresponding to formula I. A satisfactory concentration of the constituents of low boiling range was practical only with the lower-boiling and more stable acetyl derivatives of pyrethrolone. The refractive index and the terminal methyl content of the various fractions were found to be the most reliable criteria of quality, the distillation temperature having only approximate significance.

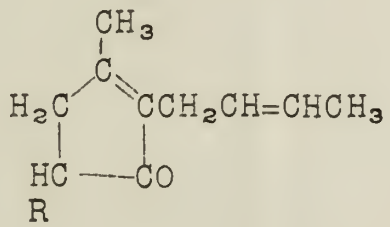
The distillate obtained by redistillation of the lower fractions of acetyl pyrethrolone furnished a semicarbazone mixture from which two members were isolated by their difference in solubility in benzene. One, m.p. 150-151°, strongly predominated and was readily soluble in benzene while the other, m.p. 151-152°, was almost insoluble and was obtained only in very small quantity.

The combined higher boiling fractions also yielded two semicarbazones which could be separated by their solubilities in benzene. The more soluble one melted at 133°, its insoluble companion at 173-175°.

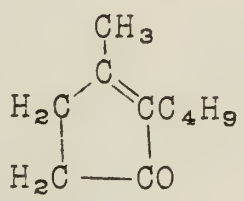
Three of the semicarbazones are represented by the empirical formula, $C_{12}H_{17}N_3O_2$, the other two by $C_{11}H_{17}N_3O_2$. The corresponding keto alcohols of the first group, $C_{11}H_{14}O_2$, have temporarily been designated as pyrethrolones B-1, B-2, and C, those of the second pair, of formula $C_{10}H_{14}O_2$ as pyrethrolones A-1 and A-2.

The only difference between B-1 and B-2 was that B-1 was optically active and B-2 proved to be the racemic mixture, while pyrethrolone C was considered to be a mixture of both the active and partially racemized compound. Thus, all three are represented by the same formula (I), which is in accord with spectrographic results indicating the presence of two chromophores. The above conclusions were based upon hydrogenation of the semicarbazones to the tetrahydrosemicarbazones followed by hydrolysis to the free tetrahydropyrethrolone, and subsequent reduction to tetrahydropyrethrone. The acetyl derivatives and acetyl semicarbazones were also prepared. Results of terminal methyl, elementary analysis and refractive index (in the case of liquids) agreed within experimental error for all of the derivatives.

Pyrethrolones A-1 and A-2 proved to be two isomeric forms, A-1 being the optically active compound and A-2 being the racemic mixture. Their relation to each other was established by a similar series of derivatives as those prepared for B-1, B-2 and C. Spectrographic data furnished by the free ketone showed the presence of only one chromophoric group. This, along with its similarity to pyrethrolone, gave rise to a compound of possible structure IX, R=OH, which was named cinerolone.



IX



X

This structure was confirmed by hydrogenation of the side chain of the semicarbazone, followed by hydrolysis of the semicarbazone and replacement of hydroxyl group by hydrogen <u>via</u> the chloro compound, which furnished dihydrocinerone of tentative structure X. The compound of this structure would be expected to furnish levulinic and valeric acids on oxidation. A convenient method was available for its synthesis through the following steps. Both the resulting 2 butyl-3-methylcyclopentenone

$$C_5H_{11}MgX + CH_3CO(CH_2)_2CO_2C_2H_5 \rightarrow C_5H_{11}\underbrace{C(CH_3)(CH_2)_2CO}_{O} \rightarrow X$$

and dihydrocinerone furnished identical values with respect to refractive index, specific gravity and boiling point. A series of derivatives of the synthetic material were prepared and their properties were found to agree with the respective derivatives of dihydrocinerone.

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